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ORIGINAL ARTICLES

NEW USES OF SPECIFIC SKIN TESTS IN CERTAIN OF THE INFECTIOUS DISEASES.[1]

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The expression "tuberculin reaction" suggests at once to our minds a current test of corroborative and marked value in clinical diagnosis. Whether the reaction elicited be general or local, we know that its appearance indicates that the individual has suffered or is suffering from a tuberculous lesion. We now understand that a positive tuberculin reaction in man probably indicates an active tuberculous process only when it is taken in conjunction with other clinical signs. In a similar way a positive tuberculin reaction in a cow does not of necessity mean that the animal is a menace to the milk supply, and it is only in the production of experimental herds that it is usually possible or necessary to kill off all reactors. At all events up to the present the tuberculin reaction has been used and can be interpreted only in respect to its diagnostic significance. We purpose discussing (1) the extension of local specific reactions like the tuberculin reaction to the diagnosis of other infectious diseases, and (2) certain other novel uses of these reactions which are of distinctly prognostic significance.

Koch's original interest in the administration of tuberculin in the tuberculous individual lay in its possible therapeutic value. This possibility has been realized, but only in a limited sense;

[1] The Samuel D. Gross Lecture of the Pathological Society of Philadelphia, October 22, 1914.

tuberculin is generally admitted to have a distinct but restricted usefulness in the cure of tuberculosis. But at the same time Koch saw and described the diagnostic uses of tuberculin. He noted the characteristic rise in temperature that follows the subcutaneous injection of tuberculin in a tuberculous animal or individual, and also the local reaction at the point of inoculation and about the tuberculous foci. But although he noted the localized reaction its diagnostic possibilities were not understood until some seventeen years later. In 1907 v. Pirquet described the simple and accurate test for tuberculosis carried out by applying tuberculin to an abrased surface of the skin (cutaneous reaction), and in the same year Calmette described an equally simple but more dangerous reaction that may be evoked in the tuberculous individual by instilling a diluted tuberculin in the conjunctival sac. These two types of localized reaction have to a large extent supplanted the generalized tuberculin test suggested by Koch.

The priority of describing a localized specific reaction in the infectious diseases of diagnostic or prognostic significance belongs, however, not to Kock or to v. Pirquet but to Edward Jenner in connection with his study of smallpox. I prefer, however, to discuss the significance of his observations in another connection.

Following the descriptions of v. Pirquet, of Calmette, and of Wolff-Eisner on the diagnostic value of localized tuberculin reactions, similar reactions have been employed in other infectious diseases. It may be mentioned categorically that the local application of the respective etiological agent has been used with more or less diagnostic success in at least hay fever, glanders, gonorrhea, leprosy, trichophytosis, sporotrichosis, and the infectious abortion of cattle. Without further discussion of these interesting results we will consider in more detail certain even more recent applications of specific localized reactions which seem to me not only of interest in themselves but indicative of a new field of usefulness.

Let us consider first the method of diagnosis proposed by Edith Claypole[2] for infections due to members of the streptothrix group of microörganisms. Dr. Claypole has found that skin tests may be employed not only to diagnose streptotrichosis differentially from tuberculosis, with which it is clinically frequently confounded, but even between members of the streptothrix group. Dr. Claypole began her work in my laboratory some three years ago with an ambitious, and I believe rather successful, attempt at a classification of the much confused group of microörganisms that may be referred to as streptotrices.[3] This group is confused not only in respect to the individuals to be included, but also in respect to

[2] Human Streptotrichosis and its Differentiation from Tuberculosis, Arch. Int. Med., 1914 xiv, 104.

[3] Claypole, On the Classification of the Streptotrices, Particularly on Their Relation to Bacteria, Jour. Exper. Med., 1913, xvii, 99.

priority of nomenclature. For reasons that are given in Claypole's paper it has seemed better to refer to them as streptotrices and the diseases they produce as streptotrichosis. Among the disease entities in man and animals that are produced by this group of organisms may be mentioned madura foot, actinomycosis, nocardiosis, and pseudo-tuberculosis. These diseases are, as a rule, characterized as slow, progressive, localized processes which are, however, capable of an acute general pyemic or pneumonic course. In her general comparison of the type organisms of this group, Claypole has shown that they run from mycelial, non-acid-fast forms through non-acid-fast or partially acid-fast bacillary forms to strongly acid-fast forms that are closely allied to the tubercle bacillus. Not only are these gradual transitions in type demonstrable from one species to another, but they may actually occur in the cultivation of a given species. A given organism may from time to time be more or less acid-fast and bacillary, or again at one time almost wholly mycelial and later bacillary. By means of antisera to the mycelial, to the partly acid-fast bacillary, and to the acid-fast bacillary types it was possible to show that neither extreme organism reacted with the antisera to the other extreme species, but that the intermediate partly acid-fast organism reacted with its own antiserum and with the antiserum to either extreme type. The acid-fast streptotrices, moreover, reacted with an antiserum to B. tuberculosis.

In a considerable number of human cases of cervical adenitis and pulmonary disease that clinically are indistinguishable from tuberculosis some form of streptothrix has been found in pure culture. I may simply mention the names of Flexner,[4] Lubarsch,[5] Ophüls,[6] Burnet,[7] and Foulerton[8] in this connection. That a distinct though unknown percentage of glandular, pulmonary, and bone tuberculosis, so-called, is due to infection with a streptothrix is becoming evident from the work of Bridge,[9] Foulerton,[10] and Claypole. Even with the examination of discharges and sputum the diagnosis is overlooked. In the presence of a non-acid-fast streptothrix the carbolfuchsin stain results in the report of "no tubercle bacilli found." On the other hand an acid-fast streptothrix, particularly if non-mycelial, is passed as B. tuberculosis. By means of Dr. Claypole's differential skin test, streptothrix infections

[4] Pseudo-tuberculosis Hominis Streptothrica, Jour. Exper. Med., 1898, iii, 435.

[5] Zur Kentniss der Strahlenpilz, Ztschr. f. Hyg., 1899, xxxi, 185.

[6] Acid-proof Bacilli in Five Cases of Pulmonary Gangrene, Jour. Med. Research, 1902, viii, 242.

[7] Streptothricee dans une adénopathie cervicale, Compt. Rend. Soc. de biol., 1913, lxxiv, 674.

[8] Streptothrix Infections, Lancet, London, 1899, ii, 779; Some Observations on a Series of Seventy-eight Cases of Streptothrix Infections, Ibid., 1913, i, 381

[9] Streptothrichosis (Actinomycosis) of the Lungs, Jour. Amer. Med. Assoc., 1911, lvii, 1501.

[10] Loc. cit.

may be readily diagnosed, and it is barely possible that when recognized they may respond to a specific treatment.

Claypole prepared solutions from two types of streptothrix, in all respects similar to old tuberculin (concentrated glycerin-bouillon growths). Her cases were all tested by the skin test of v. Pirquet with old tuberculin, with Streptotricin H. (Streptotricin Hominis, mycelial, non-acid-fast), and with Streptotricin E. (S. eppingeri bacillary, partly acid fast).

In 45 control cases which gave no clinical evidence of tuberculosis 22 reacted to old tuberculin, but none to either of the streptotricins. In 55 cases of suspected tuberculosis, comprising 42 lung, 11 gland, and 5 bone involvements, 37 reacted to tuberculin (67 per cent.); 13 of these cases reacted to Streptotricin H.; 8 to Streptotricin E., and 6 gave reactions to two of the test solutions.

Of the 13 Streptotricin H. reactions 11 were lung cases. In 9 of these no tubercle bacilli were found, but in all of them thread-like, Gram-positive organisms resembling Streptothrix H., in the 2 others, acid-fast bacilli were found as well as the mycelial organisms, and one reacted to tuberculin and one to Streptotricin E. (acid-fast), as well as to Streptotricin H. The other two positive Streptotricin H. cases were glandular; both were negative to tuberculin. In one of these cases Gram-positive segments and rods were found histologically.

Eight cases reacted to Streptotricin E., 6 with lung involvements and 2 with bone lesions; 3 of the lung cases were negative to tuberculin and had no tubercle bacilli in the sputum, without doubt infections with a less acid-fast organism than B. tuberculosis. Two of the 3 remaining cases reacted to tuberculin and to Streptotricin E. In one of these tubercle bacilli were found in the sputum. The sixth case reacted to both streptotricins and had a mycelial Gram organism and an acid-fast organism in the sputum. The bone cases did not react to tuberculin and the infections were by inference due to the Streptothrix eppingeri group of organisms.

The data from these cases should convince us that we now have a means of differential diagnosis between mycelial streptothrix infection, partly acid-fast streptothrix infections and tuberculosis. Dr. Claypole is now engaged in studying the possibilities of specific treatment in this recognizable group of streptothrix infections, in some of which vaccine treatment has already been successfully employed.

Let us next consider a form of the cutaneous reaction which is of distinct prognostic significance. Although this reaction was recognized by Edward Jenner[11] and carefully worked out by v. Pirquet[12] its significance in public health administration has,

[11] An Inquiry into the Causes and Effects of the Variolæ Vaccinæ, London, 1798.
[12] Allergy, Arch. Int. Med., 1911, vii, 259.

I believe, only recently been brought into prominence by Dr. Force,[13] of the Department of Hygiene in the University of California. We have already referred to Jenner as the discoverer of the skin reaction. We can do no better than quote the words he used in reporting his failure to inoculate fourteen persons who had previously been infected with cowpox with smallpox.

"It is remarkable," writes Jenner, "that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces smallpox. Indeed it becomes almost a criterion by which we can determine whether the infection will be received or not. It seems as if a change which endures through life has been produced in the action or disposition to action in the vessels of the skin; and it is remarkable, too, that whether this change has been effected by smallpox or the cowpox that the disposition to sudden cuticular inflammation is the same on the application of variolous matter."

This "sudden cuticular inflammation" of Jenner is recognized by v. Pirquet as "the immediate reaction" which follows attempts to vaccinate those who have recovered from smallpox or have been recently vaccinated. It indicates, in other words, that protection already exists in that individual, that antibodies are present which destroy the vaccine colony and prevent the evolution of the classical vaccine pustule. Force suggests simply that this immediate reaction be looked for in twenty-four hours and that its presence is as indicative of proper vaccination as the usual pustule which appears only at the end of several days. The presence of this immunity reaction would obviate the repeated and vain attempts to produce true vaccinia in such an already protected person.

Force and Beckwith[14] have further ingenuously employed a localized reaction of this type in the differential diagnosis of smallpox. They find that rabbits may be immunized against vaccinia or variola by subcutaneous injections of vaccine virus. Such animals show a specific local reaction on the intradermal injection of vaccine virus or of pus from a smallpox vesicle. They do not, however, react to varicella material. Force has recently been able to obtain an early diagnosis in two cases of suspected smallpox by this method.

Another skin test which may come to assume prognostic value is the luetin reaction for syphilis described by Noguchi. This reaction is produced by the local application of a preparation from a pure culture of Tr. pallidum to the abrased skin. It occurs only in cases of syphilis, and particularly in those cases in which the Wassermann reaction is negative. It occurs most frequently in late tertiary cases (80 per cent.), and becomes more intense after energetic

[13] Investigation of the Causes of Failure in Cow-Pox Vaccination, Jour. Amer. Med. Assoc., 1914, lxii, 1466.

[14] Unpublished Communication through the courtesy of Dr. Force.

antisyphilitic treatment. According to Noguchi[15] it indicates allergy, whereas the Wassermann reaction indicates an active syphilitic process. Its author further suggests that it may well be of value in indicating those cases that will derive benefit from treatment.

The Shick[16] intradermal test with diphtheria toxin, described in 1912, is of important prognostic significance. It indicates not only whether an individual has or has not diphtheria antitoxin in his blood, but very accurately whether or not he is protected from diphtheria. One-fiftieth of the minimal lethal dose of diphtheria toxin for a guinea-pig is injected intradermally in the individual to be tested. If antitoxin is present in the blood no reaction follows; if there is no antitoxin the bleb is surrounded in twenty-four to forty-eight hours by an area of redness and infiltration measuring from 1 to 2 cms., which slowly fades. It seems absolutely proved from the work of Schick and of Park and Zingher[17] that individuals who react to the irritation of the toxin have less than $\frac{1}{30}$ of a unit of antitoxin per c.c. of blood, and are not protected against diphtheria. Those who do not react are protected. The active immunity of such protected people may readily be raised by giving Behring's toxin-antitoxin vaccine. Those that give a positive reaction, the unprotected, do not respond well to active immunization and should be given antitoxin.

One of the recent interesting uses of a specific skin test is as an indication of protection against typhoid fever. The local application of extracts of the typhoid bacillus has already been tried as a diagnostic test for typhoid fever, but with indifferent success. In connection with experimental studies on methods of immunization against typhoid fever, in which my associates and I have been engaged for the past two years, many interesting questions have arisen. Dr. Claypole and I[18] have found a typhoid vaccine that produces practically no symptoms even in large doses in man, and at the same time, to judge from animal experiments, protects better than any other form of typhoid vaccine that has been described. It may simply be referred to here as the sediment of the bodies of alcohol killed, ground, sensitized typhoid bacilli from several strains. In common with many others we have found that the estimation of antibodies, particularly of the agglutinins is no measure of the degree of resistance against typhoid infection. In animals the real test of immunity is infection with the typhoid bacillus.

[15] Practical Application of the Luetin Test, New York Med. Jour., August 22, 1914.

[16] Die Diphtherietoxin-Hautreaktion des Menschens als Vorprobe der prophylaktischen Diphtherieheilseruminjektion, Münch. med. Wchnschr., 1913, lx, 2608.

[17] Active Immunization in Diphtheria Treatment by Toxin-antitoxin, Jour. Amer. Med., Assoc., 1914, lxiii, 859.

[18] An Experimental Study of Methods of Prophylactic Immunization against Typhoid Fever, Arch. Int. Med., Nov., 1914.

In the case of human beings that have been vaccinated against typhoid fever we have had no assurance that they are really protected, and still less the assurance as to how long the protection lasts. By careful tabulation of morbidity statistics we may eventually learn how long a given type of immunization protects on the average. There is no assurance, however, for the individual who may be among the unfortunate ones who have failed to respond to the treatment. Dr. Force and I[19] believe that in our typhoidin test we have found a means of indicating individual resistance to typhoid fever. We found that 41 out of 42 cases (97 per cent.), that gave a history of typhoid fever gave a positive skin reaction to a concentrated bouillon culture of B. typhosus. It may be noted that two of these positive cases had typhoid fever, forty-one and thirty-three years previously. Typhoid recoveries, it may be recalled, are to all intents thereafter protected against the disease. Repeated attacks are probably paratyphoid infections. 86 per cent. of an equal number of those that gave no history of typhoid fever gave a negative reaction. It was difficult at first to explain the 14 per cent. remaining that gave a positive test with no history of previous typhoid. We believed, as our confidence in the accuracy of the reaction grew, that these positively reacting cases may have had aborted or undiagnosed typhoid fever. This explanation is rendered probable by an observation brought to our attention by Dr. Edward von Adelung. Dr. v. Adelung was a member of a family party that visited Germany nineteen years ago. Some two weeks after they had all drunk at a suspected water source, two of the members of the party came down with a fever that ran the typical course of typhoid, and was so diagnosed. The other two had at the same time mild symptoms lasting one and three days respectively, and consisting of headache, fever, malaise and flushing, which they regarded as abortive typhoid. Neither of these latter individuals give any other history of typhoid fever. All four members give a positive typhoidin reaction.

We find that individuals that have been artificially vaccinated against typhoid give, in the majority of cases, a positive skin reaction for from one and a half to two years. It may be positive for even longer periods. There are, however, a few individuals that fail to react a few months after vaccination. This experience agrees with what we know clinically about the duration and occasional failure of typhoid immunization. We feel justified in recommending to our students that they return for a skin test a few months after vaccination and at intervals thereafter. When they fail to react they are advised to be re-vaccinated.

Our suggestion and growing belief that this skin reaction with

[19] A Skin Reaction Indicative of Immunity against Typhoid Fever, Arch. Int. Med., 1914, xiii, 471.

thyphoidin is a real measure of the protection that the individual enjoys against typhoid fever is strengthened by observations on immunized rabbits. We have already shown that the agglutinin titer is no indication of the resistance of a given animal to infection, and observations on the Widal reaction in man tend to the same belief. The typhoidin reaction, on the other hand, is positive in that category of individuals that are known to be protected against typhoid fever, namely, typhoid recoveries; it does not occur in people who give no history of the disease except in a small percentage that may reasonably be suspected of having had an abortive attack. The reaction further occurs in the majority of those that have been vaccinated against typhoid within the last two years, and then gradually disappears. We had scarcely hoped to show differences in typhoidin reaction between incompletely and perfectly immunized rabbits as tested by our method of infection, which in incompletely protected animals produces carriers, but our results in this respect have exceeded our anticipations. Normal rabbits invariably give a negative intradermal typhoidin reaction. When series of rabbits are immunized, each with a different vaccine preparation, it is found that the better protected series gives a higher percentage of positive typhoidin reactions and a correspondingly smaller number of them become infected on injection of B. typhosus.

We have taken some interest in attempting to determine the mechanism of this typhoidin reaction. The problem was inviting since so many explanations as to the cause of the tuberculin reaction have been offered. It is perhaps most generally accepted as being due to some reaction that takes place between an antigen (tuberculin) and antibodies that have been formed in the tuberculous animal. One of the disputes is as to whether the antibodies that react are concentrated in cells or circulate in the body. It has been very difficult to prove the circulating hypothesis, as the susceptibility to tuberculin has been successfully transferred by the blood to another animal in very few instances. This passive transfer has been easy to demonstrate in rabbits immunized against the typhoid bacillus. When such an animal's serum is transfused into a normal rabbit the latter becomes susceptible to the typhoidin reaction, whereas the immunized animal when transfused with normal blood loses its susceptibility. Another interesting proof of the antigen-antibody nature of the typhoidin reaction has been by the intradermal injections of sensitized (treated with immune serum) and of unsensitized typhoid vaccines in human beings. The sensitized vaccine, although it gives no untoward symptoms when used for immunization, does produce an intradermal induration and areola, the untreated vaccine does not.

In running thus hurriedly over recent applications of specific local tests I have endeavored to show that in streptotrichosis the

method serves to differentiate closely related infections, and in the case of rabbits immunized against vaccine virus it may be used indirectly to diagnose human smallpox. In the case of the Schick reaction with diphtheria toxin and the typhoidin reaction of Gay and Force, local tests indicate protection or lack of protection against the disease in question, and therefore indicate when immunization is necessary. The accelerated vaccine reaction of Jenner and v. Pirquet becomes of value as indicating protection against smallpox and the fruitlessness of further attempts at producing vaccinia.

These latter prognostic applications of localized specific reactions open up, I believe, a new field of usefulness for tests of this sort.

ON THE INDICATIONS FOR ARTIFICIAL NUTRITION.

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Artificial or extrabuccal nutrition is frequently resorted to in our medical practice. As is well known, we possess four different methods of artificial nutrition, namely: (1) subcutaneous alimentation; (2) esophagogastral alimentation; (3) duodenal alimentation; (4) rectal alimentation.

It appears of interest to broach the subject of artificial nutrition with regard to its indications and also the special methods best suited.

With this object in view, cases in which artificial nutrition may be required can be divided into three groups:

1. Cases of subnutrition in which the digestive canal presents no obstacles to the passage of food.

2. Cases of difficult or impossible nutrition caused by obstacles to the passage of food along the digestive tube.

3. Cases in which absolute rest of certain portions of the digestive tract is imperative in order to effect a cure.

It will be best to discuss the above subject in each group separately.

Group I. *Subnutrition with a Free Food Passage Along the Digestive Canal.* Subnutrition or insufficient nutrition can be observed in almost all acute and most chronic diseases. Ordinarily, however, the physician, by rational instructions and an appropriate selection of foods, succeeds in introducing by the usual way (per os) an amount of aliment sufficient for the special case.

In rare cases the introduction of an adequate amount of food becomes difficult—if not entirely impossible—by a pronounced lack of appetite or marked aversion for food. But even then the usual mode of nutrition is persisted in, provided the difficulty

of food ingestion is merely temporary, *i. e.*, lasts a few days. So soon, however, as the insufficient nutrition is protracted, and attempts to overcome it by the diverse means at our disposal fail, the necessity of artificial nutrition makes itself felt. In complete abstinence from food artificial nutrition will be the more demanded.

As a whole, total food abstinence is met with principally in the insane and melancholics, also in several severe affections of the central nervous system, while insufficient nutrition is found in chronic diseases of the most various types.

With regard to the selection of the special kind of artificial nutrition in this group, the esophagogastral method will be selected. For the aliment is undoubtedly best utilized when subjected to the work of the entire digestive apparatus.

In case the repeated insertion of the stomach-tube is especially annoying to the patient, the duodenal tube may be used instead, provided the patient is not rebellious to treatment. In this instance the capsule at the end of the tube should best be made of gold, platinum, or hard rubber. The same method as that of duodenal feeding is applied with the difference that here the end of the tube with the capsule may remain in the stomach. The length of the tube in the digestive canal from the lips should be about 54 cm. The duodenal tube is, therefore, fastened in such a manner that mark II is situated outside the mouth. The thin tube does not molest the patient and is left in the digestive tract for about two weeks.

The food substances here used are, likewise, identical with those in duodenal alimentation, with the difference that larger quantities may be injected at each feeding.

Whereas in absolute food abstinence the total quantity of aliment is given through the tube, in insufficient nutrition one proceeds somewhat differently. As much food as possible is administered by the mouth, and what is still lacking is given by the tube. As soon as the patient ingests a sufficient amount of aliment by the mouth, artificial nutrition is stopped.

GROUP II. *Difficult or Impossible Nutrition Caused by Obstacles to the Passage of Food along the Digestive Tube.* This group represents the largest number of cases in which artificial nutrition is employed. It may be advantageously split into two subdivisions: (*a*) Organic stenosis of a high degree (including malignant stricture even of a minor degree); (*b*) medium-sized benign organic stenoses and spastic strictures.

(*a*) Difficulty in the passage of food caused by marked stenoses of the esophagus, cardia, pylorus, duodenum, or small intestine demands *rectal alimentation*. The same obtains if the difficult passage along the above localities is caused by pronounced obstacles compressing the digestive tube from without or by malignant stenoses of any degree.

Similar stenoses along the colon require *subcutaneous alimentation*.

In all these cases artificial nutrition is but a temporary adjuvant, and the stricture requires separate treatment, whenever possible. Thus in benign stenoses, when feasible, stretching should be performed; in malignant strictures, or in benign stenoses either not yielding or not accessible to stretching, likewise in tumors pressing from without an operation for the radical removal of the trouble should be undertaken.

In case the latter is impossible one must be satisfied with the surgical reëstablishment of a food passage, making nutrition possible. Thus in obstacles along the esophagus and cardia a gastric fistula, in those of the pylorus and duodenum a gastro-enterostomy, in those of the small intestine and colon—according to the location of the obstacle—an entero-enterostomy or enterocolostomy, or colocolostomy, or ultimately an *anus preter-naturalis* should be established.

In case an operation for some reason or other is unfeasible, artificial nutrition will naturally have to be carried on as long as life persists.

In these instances subcutaneous and rectal alimentation can be to advantage conjointly employed, or, if necessary, used alternately.

(*b*) *Medium-sized Benign Organic Stenoses and Spastic Strictures of the Digestive Tract.* In obstacles to the food passage due either to benign organic stenoses of a moderate degree or to spastic conditions—the selection of the special mode of nutrition will depend upon the location of the difficulty.

In spastic states of the esophagus and cardia—provided they are of such a high degree that the usual mode of nutrition be entirely impossible—and in moderate-sized stenoses of the same regions, gastral nutrition by means of a somewhat thin stomach-tube will be employed. In moderate benign strictures of the pylorus, or duodenum or in spasm of the pylorus, duodenal alimentation will be resorted to. If the latter for some reason or other fails, rectal alimentation will be used instead.

Stenoses of the small intestine—interfering with the prochoresis to such a degree that complications endangering life begin to appear—require rectal alimentation. If the affected area is situated in the colon, subcutaneous alimentation should be instituted.

In the whole subdivision (*b*) the separate treatment of the principal lesion should, likewise, never be lost sight of. The artificial nutrition is but a temporary adjuvant, and should be employed until the obstacles—if this be possible—have been removed or the natural mode of nutrition reëstablished.

GROUP III. *Absolute Rest of Certain Portions of the Digestive Tract is Imperative in Order to Effect a Cure.* In this entire group the ordinary way of nutrition, while at times somewhat impaired, is, however, always possible. The extrabuccal alimentation is here employed as a means of curing or ameliorating diseased states.

This group may be suitably divided into two parts: (*a*) diseased states of the digestive tract proper (exclusive of stenoses); (*b*) diseased states of other organs situated without the digestive canal.

(*a*) *Diseased States of the Digestive Tract Proper* (*Exclusive* of *Stenoses*). Severe inflammatory processes, injuries, and ulcerations of the digestive apparatus often demand perfect rest of the affected part in order to achieve complete recovery. This, however, is possible only then when the food contact is entirely removed from the diseased area.

If the lesions just named involve the mouth, pharynx, or esophagus, gastral alimentation by means of a stomach-tube or a thin tube *à demeure* will be resorted to.

In case the seat of the lesion is located in the stomach or duodenum, duodenal alimentation will be employed. It is self-understood that in affections of the duodenum the capsule end of the tube will have to lodge about 5 to 10 cm. or still more below the diseased part. In fresh hemorrhages of the esophagus, stomach, or duodenum rectal alimentation is best administered during the first two or three days, and then duodenal alimentation instituted. Ulcers of the stomach and duodenum have been particularly benefited by this mode of treatment. Besides in the affections just mentioned duodenal alimentation can be employed to great advantage in the following conditions: dilatation of the stomach (due to weakened musculature) and severe neuroses accompanied by persistent vomiting.

In case the above lesions (described at the beginning of this group) are situated in the small intestine, rectal alimentation is employed, if needed—and if located in the colon—subcutaneous alimentation. It is self-understood, however, that in the last-named instances artificial nutrition will be resorted to merely as an extreme measure, for neither rectal nor subcutaneous alimentation, nor the two combined, are able to supply adequate nutrition to the organism.

(*b*) *Diseased States of Other Organs Situated Without the Digestive Canal.* At first sight it appears rather strange that artificial nutrition should be indicated in diseases of organs not participating directly in the act of digestion. If we consider, however, what intimate relations exist between the digestive apparatus and the organs of circulation as well as of elimination—with each ingestion of food there is an overflooding of the circulation with new material and as a consequence an augmented activity in the circulatory and eliminative systems—it is plausible that leniency toward the digestive tract will exert a beneficial influence on other remote organs.

In fact it has been long known that a scanty insufficient nutrition, as, for instance, "Karell's diet," applied for a short period, is of distinct benefit in disturbed compensation of the heart.

Occasionally the ingestion of the smallest amount of food into the stomach produces an irritative state of the neighboring organ, the heart, especially if the latter is badly diseased. In such instances artificial nutrition (rectal or duodenal alimentation) may be indicated.

In two cases of severe myocarditis causing stenocardia in a high degree—and in which the minutest quantity of food given by mouth brought on attacks of severest dyspnea greatly endangering life—I have seen duodenal alimentation applied without the slightest inconvenience to the patient. This mode of nutrition greatly alleviated the condition of the two patients and prolonged their life.

There is, therefore, an indication for artificial nutrition in severe affections of the heart in which the ordinary mode of alimentation is accompanied by severe dangerous symptoms. Rectal or, still better, duodenal feeding will then be used.

Diseases of the liver occasionally require a course of artificial nutrition (rectal or, still better, duodenal alimentation), in order to relieve somewhat the functions of this important organ. In several cases of cirrhosis of the liver[1] I have observed the greatly beneficial influence of duodenal alimentation on this disease.

CONTINUOUS CLONIC SPASM OF THE LEFT ARM (EPILEPSIA CONTINUA) CAUSED BY A TUMOR OF THE BRAIN.

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The title describes the symptom of greatest interest, others, less important but still noteworthy, are brought out in the history.

The patient, an American housemaid, aged fifty-six years, unmarried, was admitted to the Philadelphia Home for Incurables in 1902. In 1897 she had noticed a swelling in the right breast which proved, a year later, to be a carcinoma. The breast was then amputated, but the growth recurred in the scar, and in consequence she was admitted to the Home and for several months nothing unusual happened. Then the patient noticed slight muscular twitchings in the left arm, recurring ten to twenty times daily and continuing from a few minutes to half an hour. In addition she complained not only during the attacks but also in the intervals between of a weakness in the left arm unaccompanied by pain. A week after the onset of the twitching she had an attack of Jacksonian

[1] Max Einhorn, On the Beneficial Effect of Duodenal Alimentation in Cirrhosis of the Liver, Medical Record, July 26, 1913.

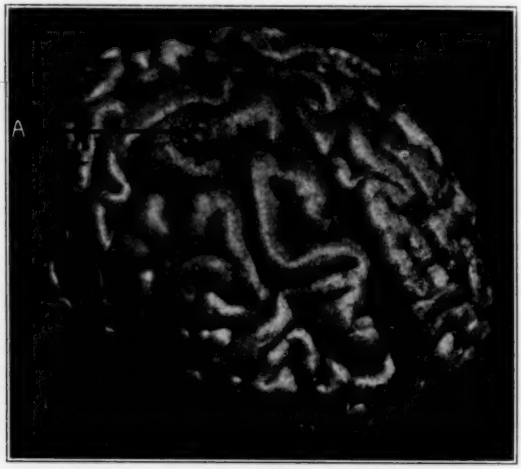
epilepsy. It began on attempting to pick up something from the floor with the left hand. The arm was involuntarily jerked upward above the head while the forearm was flexed to a right angle. An attendant, who was standing by, tried to lower the arm, but was unable to do so on account of its rigidity. Violent clonic convulsive movements instantly began in the arm and continued for about ten minutes without involvement of any other part of the body, except that both eyes rolled and the eyelids on both sides quivered. The patient was greatly frightened by the attack, and while it lasted screamed, paid no attention to commands, would not listen to questions, or make any attempt to explain how she suffered. Her excited state was evidently caused by loss of emotional control, mere fright, but after a short time she certainly became dazed, if not indeed absolutely unconscious, for a minute or two. After the attack was over she had only a vague recollection of what had happened (not entirely because of amnesia but partly from lack of attention caused by fear), and for about a quarter of an hour complained of complete loss of power and sensibility in the arm. She rubbed and pinched the arm vigorously, saying, "My arm is dead. I have got no feeling in it." For the following three or four hours there was nystagmus in both eyeballs and palsy of voluntary movement of both internal recti muscles. During the following two weeks she had five similar atacks of Jacksonian epilepsy, all of them immediately following voluntary movement of the arm, but many times she used the arm without any convulsion occurring. In other words, while voluntary muscular effort was a factor in precipitating an attack it was not the only factor, because most of the time she could use the arm perfectly well without any consequent convulsive effect. She never had any more attacks like these six, but the twitching of the arm became more and more frequent until, after a few weeks, it was practically never still during waking hours, but was constantly twitching and jerking, not severely, but enough to make it useless. She would sit all day with the arm flexed at the elbow and fastened to the arm of a chair by wrapping both in a shawl, claiming that the warmth and fixation relieved somewhat the constant twitching. Toward the end the twitching did not cease even during sleep, and if, while asleep, she made any large unconscious movement of the arm the twitching became so severe as to waken her. This was seen many times by her attendant, who watched her closely. In addition to the muscular contractions, causing movements of the arm, there were frequent, slight, spontaneous contractions of individual muscles not strong enough to move it. Contractions of single muscle bundles never occurred; either many, several, or only one muscle might contract at any one momemt, but never a part of one muscle. There was never any fibrillary twitching. Tapping any muscle in the arm caused local "humping" and increased the already present twitching

or brought it on if absent. There was no muscular wasting, but distinct loss of voluntary power seemed to be present for some weeks before death, though it was difficult to demonstrate, because by that time any attempt on the patient's part to use the arm brought on extremely severe spasmodic movements, and it was almost impossible to distinguish voluntary from convulsive movements. The biceps and triceps jerks in the left arm were very marked, but it was impossible to obtain them on the right side, owing probably to the extreme edema resulting from the carcinoma. Sensibility to pain, touch, and temperature were normal over the whole body, except that the swollen right arm was slightly less sensitive to touch than the left. A painful stimulus on the left arm increased the twitching, but mere touch did not. Though the patient never complained of any trouble in the left leg, never even mentioned it, occasional slight spasmodic twitchings were visible in it. They were not severe enough to interfere with walking, and there was no loss of power in either leg. The left knee-jerk was larger than the right, but there was no Babinski jerk, indeed no plantar jerk of any kind, and no ankle-clonus. The patient did not complain of any of the characteristic general symptoms of brain tumor—neither headache, vertigo, nor vomiting—and optic neuritis was absent. She rapidly failed on account of the progress of the carcinoma, and in about twelve weeks after the first appearance of the twitching in the arm died.

The diagnosis was metastatic carcinoma of the brain, and the necropsy revealed the following condition: The right ascending frontal convolution was quite a little larger than the left and on its surface, about 4 cm. from the longitudinal fissure, projecting a little from the surface, was a tumor about the size of a large pea, growing from the pia-arachnoid and pressing into but not destroying the cortex. The tumor was shelled out with ease. There was another similar mass about the same size on the inferior surface of the left lobe of the cerebellum. Microscopic examination showed the two tumors to be carcinomatous. The illustration shows well the size and location of the first-mentioned growth. Though the right ascending frontal convolution was larger than the corresponding ascending parietal, caused apparently by local edema (no overgrowth of connective tissue or any foreign cells being present in it), the difference is unduly great in the picture because of fore-shortening.

It is not unusual to find at necropsy in cases of carcinoma more or fewer secondary growths scattered over the brain. As a rule they are so small or so situated as to cause no cerebral symptoms. Less frequently the tumor is so large as to produce all the general symptoms, or so situated as to cause definite symptoms of focal disease. We have no accurate statistics in this country concerning the frequency of secondary cerebral involvement in cancer, because it is not customary to examine the brain in such cases, unless there

are cerebral symptoms, and not always then. We have no knowledge as to how often there are small cerebral metastatic growths without cerebral symptoms, but judging from European statistics the association is very frequent.



Small pial metastatic carcinoma in the right ascending frontal convolution. *A*, indicates tumor.

It is unusual for a tumor to be situated just where it will produce the symptoms occurring in this case, and for death to ensue, from carcinomatous intoxication, before the tumor has grown enough to cause destruction of tissue. There are several interesting problems involved in explaining the case. Though the tumor was the cause of the cerebral symptoms, other factors than mere mechanical pressure must have acted, because it was constant, or rather slowly increased over a period of months, while for a long time the twitching movements were intermittent, *i. e.*, there were times when the twitching ceased entirely. At the end, when the twitching in the arm was constant, it is to be presumed that the motor cortical cells were continuously irritated by the tumor itself and by the slight localized pia-arachnoiditis around it. (There was a small area about as large as a dime around the tumor the seat of meningitis.) It is probable that the Jacksonian fits which occurred early in the course of the illness were precipitated by sudden alterations in blood-pressure acting on cells just ready to explode. The fact that voluntary movement of the arm produced, or if they were already present, increased the twitchings is probably to be explained in the same way—the cells were so irritated mechanically by the tumor that the slightest increase in excitation set them off.

The total absence of sensory disturbance, except for a short time after the Jacksonian fits, is interesting, and is of some value in deciding the exact boundaries of the cortical sensory centre. It would seem that in this patient the part of the anterior ascending frontal convolution invaded by the tumor, and presumably the entire convolution, had no sensory function. The transitory anesthesia after a Jacksonian fit is of no value in localizing sensibility. The common view today is that the ascending frontal convolution is entirely motor, but it may be that there are individual differences in the boundaries of sensory representation. This would explain the differences in the findings of different observers.

Several cases of continuous twitching of an arm or a leg or both have been reported. So far as I know Kojwenikoff was the first, in 1894, to give the condition a name, epilepsia continua. He reported four cases, none of which came to autopsy, and drew the following conclusions. In all his cases, he writes, the duration of the phenomena and their unilateral distribution indicate a lesion of the cortical cells, and since brain abscess, syphilis, edema, embolism, and brain tumor were excluded, he concludes that the cause was encephalitis with sclerosis. Kojwenikoff's conclusions were based entirely on his own four cases, and he does not speak of cases like mine in which a small tumor was the irritant. Oppenheim, in his text-book, refers to a case of tumor of the leg centre he had seen in which ryhthmical twitching of the toes continued for four days. He also speaks of clonic facial spasm occurring in a case of tumor near the facial centre. A few other authors refer to the matter.

Epilepsia continua is not a thing in itself, not a disease, but a mere symptom, and occurs as a result of many conditions; indeed, anything continuously irritating the motor cortex may cause it. If the irritation be local the twitching will, as a rule, affect only one part of the body, though sometimes a localized lesion may cause a widespread explosion: if the irritating lesion be very diffuse, then the twitching may be universal. Thus it is not unusual in well-developed cases of paresis to see twitching confined to one leg or arm, or involving all the extremities and even the face, depending upon how widespread the cortical disease is. Much more rarely the twitching may appear at the onset of the disease and precede marked mental symptoms. The tremor of the tongue on extension and of the corners of the mouth on talking, which often appears in the early stage of paresis, is really similar to epilepsia continua, and is caused by superirritability of the motor cells. Later the tremor becomes a continuous twitching. In so-called myoclonus epilepsy the movements occurring between the convulsions are, as a rule, very coarse, but even in it there may be only twitching. Indeed, many types of movement disorder may occur in epileptics. In one case, for example, for about six weeks before death in status epilepticus, there were periods between the convulsions when the

patient had the movements of St. Vitus' dance, and at other times showed athetosis in both arms and legs, and at still others merely the twitching of epilepsia continua. The explanation of this variability in type of motor disorder probably is that the character of the movements depends largely on the intensity of the irritation as well as on the area covered by the lesion.

The important thing in diagnosing the condition is to find the underlying cause. The diagnosis of brain tumor in my case was based entirely on the occurrence of the symptoms of a focal brain lesion in a person suffering from carcinoma. It is always safe to diagnose cerebral metastasis in any case of carcinoma in which cerebral symptoms occur if hemorrhage and thromosis can be excluded. The absence of choked disk, cerebral vomiting, vertigo, and headache do not exclude tumor, carcinoma, or any other malignant growth being present elsewhere in the body, and the presence of focal symptoms points strongly toward it because the classical symptoms of tumor occur only when the growth has attained some size, but a very small tumor may cause focal symptoms if situated in any part of the cortex having specialized functions.

PULSUS ALTERNANS.

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In 1872 Traube, in an admirable article, directed attention to a hitherto undescribed condition of the pulse, with rhythmical irregularity in volume, which he called pulsus alternans, the sphygmogram showing waves of large and small amplitude, following each other in regular succession. He also noticed in the case which he described that while large and small beats were placed alternately throughout, the interval whjch separated the large from the small beats exceeded that which separated the small from the large beats. He further observed that the rhythm of the heart's action was perfectly normal.

Despite this early publication of Traube no other case of a similar character was recorded until 1892, when Sansom, in his book on the *Heart and Aorta*, refers to a case of cerebral hemorrhage, Cheyne-Stokes respiration, and general arteriosclerosis, with radiograms showing typical pulsus alternans. He states that the peculiar derangement of the rhythm of the pulse as seen in the sphygmogram was not at any time detectable by the finger. It is an example of alternating pulse, a more ample one being always succeeded by a less ample tracing, each beat being perfect in all

its elements, the irregularity being in volume only, and the cyclic sequence being invariable. Sansom says, to explain the large followed by the small pulse, we must assume that the ventricle delivers a full content in the large beat and an imperfect content in the small beat. The nervous mechanism which regulates this occurrence is the vagus. The lesion affecting its origin in the floor of the fourth ventricle is one which, calling into play its function of inhibiting the heart's movements in slight degree, is insufficient to elongate the diastolic pause, but antagonizes the sympathetic incompletely, so that this influence of the latter comes into play too soon in every alternate cycle. He also refers to another case of clinical alternation occurring with the onset of Cheyne-Stokes breathing. Hering believes that both the experimental and clinical alternation is to be explained on the hypothesis of a hyposystole or partial asystole. He has observed in the exposed hearts of lower animals that under pathological conditions all the heart muscle fibers are not in the same degree of contraction; that during the smaller beat of alternans, different degrees of contraction of the ventricle occurred. In this study Hering also showed that when tracings were taken from the clinical apex, or apex of the left ventricle in animals, the larger wave of the cardiogram corresponded to the smaller wave of the radiogram, thus producing a distinct incongruity between the apex beat and the pulse curve. On the other hand, when the cardiogram was taken from the third left intercostal space, or over the body of the right ventricle, the highest upstroke of the cardiogram corresponded to the strong beat of the radial. These results were constant and repeatedly observed. After the death of the animals needles were inserted through the intercostal spaces at the points where the cardiograms were taken, and on opening the thorax it was found that the needle in the fifth intercostal space was lodged in the left ventricle just above the apex. The needle in the third intercostal space was found in the conus of the right ventricle.

Hering believes that this incongruity between the cardiograms from the apex and those from the conus region, and the radiograph curves in alternans shows that the musculature which causes the apex beat has little or no propelling effect on the contents of the left ventricle. He further states that alternation is due to a disturbance of contractility without disturbance of rhythm, rapidity of rate, or lack of stimulus production, but is dependent on pathological changes in certain areas of the myocardium, the smaller beat being an evidence of the fact that the diseased areas of the myocardium react to stimulus production but slightly or not at all.

These observations of Hering were verified and somewhat elaborated by Rihl, who in 1906 reported 4 cases of clinical alternation, with two autopsies. All 4 cases were accompanied by general arteriosclerosis, chronic myocarditis, and hypertension. In the

3 cases that came to autopsy marked myocardial changes were found associated with general arteriosclerosis and chronic interstitial nephitis. In one case the coronary arteries were greatly sclerosed and the seat of aneurysmal dilatation. Rihl found the cardiac rhythm perfectly normal. He found that the height of the apex differed, a large and small beat following each other in regular succession. This shows alternation in the left ventricle. None of his cases showed evidence of alternation of the auricles. In all his cases an occasional extrasystole was observed, after which in each instance the alternation was more pronounced. He also found that anything that caused the heart to beat more rapidly, such as walking or other exercise would make the alternations more marked.

In 1905 Volhard discussed clinical alternation, and published 2 cases of true pulsus alternans and 2 cases of pseudopulsus alternans or continuous bigemina. The cases of true alternans were in young men, one a case of mitral stenosis with decompensation, aged twenty-seven years, and the other a case of chronic Bright's disease with albuminuric retinitis, aged twenty-five years. Both died within a few weeks after entering the hospital. His conclusions were that in man cardiac alternation is due to variation in strength of the contraction of the auricles as well as the ventricles; that the change in the pulse is due to difference in volume and that the cardiac rhythm is absolutely normal; that the smaller wave of alternans is due to the weakened contraction of the small systole plus the high aortic pressure; that with extrasystoles the alternation is very much pronounced; that continuous bigemina, or pseudopulsus alternans, resembles closely true alternans, but may be distinguished by the long compensatory pause following the small wave, and the small wave occurring at its normal time period.

Engleman has shown from experiments on lower animals that alternation is due to disturbances of contractility and not conductivity. Wenckebach is of the same belief and divides pulsus alternans into two forms: In one the time of the small wave exceeds that of the large, and the other in which the time interval of the small wave is the shorter. The first form he explains by the fact that the small wave is transmitted more rapidly into the aorta than is the larger; and the second form, with the large time interval of the small wave, by the hypothesis that alternation is due to weakened or exhausted contractility.

Hoffman believes that, owing to the disturbed function of contractility existing in alternation, contraction occurs more quickly than normal, and hence the periods of time of the systole and diastole are necessarily both shortened. In other words the heart muscle reaches the point of maximum contraction and relaxation much more quickly than in health.

Mackenzie, in his book on *Diseases of the Heart*, second edition,

states that a striking and characteristic sign of exhausted contractility is sometimes seen in the size of the pulse beat. He further states that "I have repeatedly dwelt upon the fact that the deviation and force of contraction depend in a measure on the length of the preceding period of rest. In hearts with good contractility, recovery after a contraction is so rapid that little or no difference can be detected in the size of the beat after pauses of varying duration. In cases of exhausted contractility, on the other hand, recovery is slow, so that the size of the beat has a distinct relation to the length of the preceding diastolic pause. This is exemplified in cases of extrasystoles. In those with good contractility the succeeding beat following the compensating pause may not be much increased, or may be very large, and the succeeding beats may be almost uniform in size. Whereas the same phenomenon occurring in hearts with exhausted contractility, the large beat following the diastolic pause, may be followed by several smaller beats of varying size in regular alternation. This difference in the size of the beats is an important one, as it indicates a grave exhaustion of contractility. Not infrequently the difference in the size of the beats persists for a shorter or longer period in such manner that the large beat alternates with the small beat, the pulsus alternans.

Mackenzie explains the pulsus alternans as follows: When contractility is depressed, if time be allowed for a full and strong contraction, the longer duration of contraction encroaches upon the period of rest, so that by the time the next stimulus arrives the contractility has not sufficiently recovered and a smaller and shorter contraction occurs. As this contraction is shorter in duration the period of rest is thereby lengthened before the next stimulus arrives, so that the contraction would be stronger and larger; being larger it will again encroach upon the period of rest and the process of alternation goes on.

Of the more recent studies on this complex cardiac mechanism those of Davenport, Windle and Thomas Lewis are instructive and interesting. Windle states that pulsus alternans is properly given only to that form of pulse in which a strong beat is regularly followed by a weaker one, the duration of the pulse periods being generally equal, although at times there may be slight alternation in the rhythm of the beats as well as in the force; but the difference in duration from one pulse to the next is small, and invariably the larger period belonging to the stronger beat, the weaker beat being therefore slightly delayed. From the polygraphic curves taken from his twelve cases, Windle states that he observed but one example of alternation of the clinical apex, while in all disparity in force of alternate radial pulses was decided and at times extreme. In the exceptional case the stronger beat of the heart curve coincided with the weaker one of the pulse. Thus this example confirms

Hering's observations. He also offers in explanation of this apparently incongruous phenomenon, Hering's theory that the musculature which forms the apex is not concerned in propelling the ventricular contents into the aorta. In this latter case alternation was often pronounced in records of the jugular pulsation; invariably the large *a* wave corresponded to the higher of the radial pulse beat. He observed no variation in intensity of the pitch or duration of the heart sounds or murmurs coincident with alternation of the pulse. His observations lend support to the view of Hering that alternation of the heart beat may be due to a partial systole of the ventricle. Lewis states that heart alternation occurs under two circumstances: (1) when the cardiac muscle is not altered structurally, as an accompaniment of great rapidity of rate; (2) when the pulse is of normal rate and under such circumstances the muscle is markedly degenerated.

Lewis' experiments were upon rabbits with ligature of the coronary arteries. He found that obstruction of one or other coronary artery was followed by rapid and new rhythms arising in the ventricle, the ventricular rhythm dominating that of the cardiac chambers, and that if the heart rate is greatly increased, alternation frequently appears both of the ventricles and auricles independently. As a result of these experiments, Lewis observed a divergence between the alternation in the ventricle and carotid, and explains this phenomenon on the coexistence of alternation in the force of the auricular contractions, thus supporting the view of Volhard, whose tracings showed that the large apical curve corresponded to the smaller radial beat alternation occurring in the amplitude of the *a* waves in the jugular, the small radial beat being preceded by the small *a* wave.

Lewis further states that the electrocardiographic curves obtained in clinical alternation are similar to those obtained experimentally, there being a divergence between the heights of *R* and *T* waves and the amplitude of the radial upstrokes. These facts demonstrate the identity of clinical and experimental alternation.

From a careful survey of the above-mentioned observations one is led to the opinion that both clinical and experimental alternations is the result of varying degrees of impairment from exhaustion of that most important function of the myocardium, contractility, which may be due to temporary exhaustion from the overwork of great rapidity of action or to permanent exhaustion and early cardiac failure, the result of grave pathological changes in the myocardium. The sequence of events of contraction of the cardiac chamber in alternation is normal. There is no defect of conductivity and the myocardium responds to stimulus production. The only abnormal rhythm is the variation in volume of the pulse beats and ventricular output, each large beat being succeeded by a smaller one, and so on indefinitely. This variation in amplitude

of the pulse beat, which is an evidence of exhausted contractility is of itself, owing to the lack of time interval between the small and large beat and the greater interval between the large and small beat, a menace to the further restoration of this function, because of the marked shortening of the preceding diastolic pause, which is so essential to a full restoration of the function of contractility. It is this shortening of the diastolic pause in all cases of long-continued tachycardia that results in early cardiac exhaustion.

FIG. 1.—Pulsus alternans, with an occasional extrasystole. S. B. P., 230; D. B. P., 170. Chronic interstitial nephritis, chronic myocarditis, and general arteriosclerosis. Note the time interval of the small wave is the same as that of the large wave, $\frac{1}{5}''$.

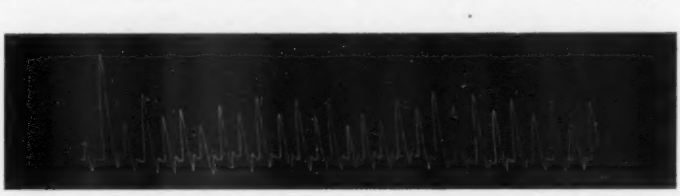

FIG. 2.—Paroxysmal tachycardia which continued six days, showing the alternation of acute myocardial exhaustion.

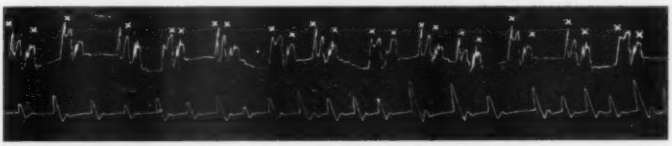

FIG. 3.—Pseudopulsus alternans, or continuous bigeminy due to extrasystoles. Mitral stenosis and regurgitation.

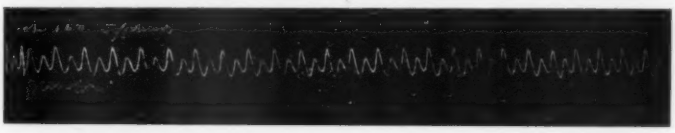

FIG. 4.—Dicrotism resembling clinical alternation, second week of typhoid.

Temporary exhaustion of contractility often occurs with the production of a typical pulsus alternans from an overtaxation of the cardiac musculature, the result of a too rapid rate, such as may occur in paroxysmal tachycardia, auricular flutter, auricular

fibrillation, or the long-continued tachycardia which accompanies Graves' disease. Experimentally it may be produced in healthy hearts by electrical stimulation, the injection into the bloodstream of digitalis, antiarin, aconitin, glyoxylsäure, and hemolytic serum. It is most frequently encountered, however, when the heart is beating within its normal rate, and when it denotes a grave pathological condition of the myocardium, with failing contractility. Most of the observed cases of this type of pulsus alternans have occurred in patients with general arteriosclerosis and hypertension, associated with chronic myocarditis and chronic nephritis. It frequently comes on during a period of Cheyne-Stokes respiration and continues to the fatal issue. It is usually not observed, however, until compensation is failing and the heart chambers are suffering from dilatation, the heart fibers having undergone both fibroid and fatty changes. It is not at all uncommon in the greatly dilated hearts of mitral stenosis or insufficiency where decompensation has occurred. It also occurs during and directly after recurring attacks of angina pectoris. Mackenzie has reported a notable example of this sort, and one of the five cases of clinical alternation which have recently been under my observation occurred after a repetition of attacks of angina pectoris, and lasted but a week, when the myocardium gradually failed and the patient succumbed. In this case the systolic blood-pressure was always under 140 mm. Hg. Alternation frequently comes on during a period of Cheyne-Stokes respiration and then continues to the fatal issue.

The relation of extrasystoles to alternation is most interesting and of great practical importance; in fact, many cases of regular bigemina have been confused or mistaken for and described as true cases of pulsus alternans. This so-called pseudopulsus alternans, or continuous bigeminia, may be distinguished from true alternans by the long-time interval, diastolic or long compensatory pause following each small or extrasystolic beat, and this in turn being followed by a larger beat, while the small beat has its normal time interval; whereas in true pulsus alternans the longer period follows the large beat or the large and small beat are equidistant from each other.

In a large number of my tracings showing extrasystoles, alternation has frequently succeeded for a single or a number of beats, the large wave following the long compensatory pause after the extrasystolic contractions, thus showing a decided impairment of the function of contractility. In many of the recorded cases of true alternation an occasional extrasystole is interpolated, and following such extra beats the alternation immediately becomes more in evidence. Not only may alternation follow extrasystoles, but, as shown by Windle, it often precedes the extrasystolic contractions. Several such examples have come under my observation. While I do not ordinarily regard the appearance of extrasystoles as of evil prognostic import, I do so regard those extrasystoles

which by repeated observation are found to be invariably followed by alternation extending over a considerable period of time. In two such examples of my own, death has occurred from decompensation and failing myocardium within two years.

Of the 5 cases of clinical alternation which have been under my care for the past two years, 3 have died—one at the age of seventy-eight years, of failing heart, following a series of attacks of angina pectoris, resembling a true anginoid status, with the clinical evidences of general arteriosclerosis and chronic nephritis, without hypertension. One died suddenly, when aged sixty-eight years, of general arteriosclerosis, high blood-pressure, chronic nephritis, and chronic myocarditis. A third, a man, aged forty years, died with all the evidence of decompensation, Cheyne-Stokes breathing, and uremia, the blood-pressure remaining high until near the end. The alternation in this case was first observed at the onset of the altered respiratory rhythm. The 2 cases now living are clinically typical examples of interstitial nephritis, general arteriosclerosis, hypertension, and chronic myocarditis. The older patient is aged seventy-two years and the other fifty-two years.

In 4 of these cases it was impossible to detect by palpation of the radial pulse the slightest evidence of alternation nor could one perceive by palpation of the clinical apex the slightest evidence of such a condition. In one case, however, the variation in volume between the large and small beat was so great that palpation of the radial was highly suggestive, although not positive, of alternation. The small beat resembled so closely the secondary wave in dicrotism that I was unable to distinguish between it and alternation until radiograms were taken. I therefore believe that palpation alone of any artery, radial or carotid, is a poor index of the presence of alternation or of the condition of the true action of the heart or of the height of the blood-pressure. I do believe, however, that defects of contractility from myocardial degeneration in the permanent irregularity of auricular fibrillation, or continuous bigemina, may be detected by comparing the rate of the radial pulse with that of the apex beat, determining the latter either by palpation or ausculation, and noting the deficit between the rate of the apex and that of radial. It is no uncommon observation to find that a third or half of the systoles of the left ventricle fail to be registered at the wrist. Many of the systolic contractions are so feeble that the intraventricular pressure does not overcome that of the aorta, and therefore the aortic valve is not lifted. If, however, the aortic pressure is overcome the pulse fails to reach the wrist because of the high blood-pressure plus the peripheral resistance.

In my cases of alternation no change in the intensity, pitch, or quality of the heart sounds were detectable. An extra or interpolated third sound was never heard. In one case, with a relatively loud systolic apex murmur, no change in its timbre occurred. In 3 cases no marked alternation was observed in cardiograms taken

from the clinical apex. In 2 cases, however, such alternation was very distinct. The respiratory excursions, because of the dyspnea in individuals with myocardial insufficiency, is so great that it is often difficult without temporary cessation of the respiratory act to get satisfactory cardiograms. In all cases the rhythm of the heart's action was normal. In three of the cases where satisfactory phlebograms were obtained the *a–c* interval was not increased, showing that conductivity was normal.

From this study the following conclusions may be drawn:

1. That pulsus alternans, while not common, is not very rare. I agree with Mackenzie and Windle in giving it the third place among pulse irregularities, extrasystoles being placed first and the persistent irregularity of auricular fibrillation the second.

2. Clinical alternation is frequently overlooked because it cannot be recognized without the graphic registration of the pulse.

3. Its presence is positive evidence of defects of the function of contractility, this in turn being due to temporary or permanent myocardial changes.

4. From a prognostic stand-point the presence of pulsus alternans, save the temporary form, due to great rapidity of rate, is grave, as it indicates extensive myocardial degeneration, most patients dying from cardiac insufficiency within three years of its onset.

5. Extrasystoles, invariably followed by alternation, also indicate exhaustion of contractility and carry with them a grave prognosis.

6. Persistent false bradycardia, due to feeble systoles, where the deficit between the apex beat and the pulse rate is but little altered by the exhibition of cardiac tonics, such as digitalis or strophanthus, also indicate grave defects of contractility, with extensive myocardial degeneration and unfavorable prognosis.

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WHAT FACTS OF DIAGNOSTIC OR PROGNOSTIC VALUE CAN BE DETERMINED FROM TEST-MEAL EXAMINATION OF PATIENTS WITH GASTRIC SYMPTOMS?

A CLINICAL ANALYSIS OF 7041 CONSECUTIVE CASES EXAMINED BY A UNIFORM METHOD.[1]

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The work forming the basis of this report was personally performed in my services at the Mayo Clinic and at Augustana Hospital. A close association of clinical, laboratory, and operative observations was possible in 7041 consecutive patients. Independent records were kept of histories, analytical data, and pathological findings. When the individual case had been finally disposed of the facts determined independently were grouped. In this way, unbiased, non-subjective information was assured.

The patients of this series came on account of self-styled "dyspepsia" or "indigestion," or, in the routine history taking, symptoms were elicited which pointed to some primary or secondary gastric disturbance. Their ages ranged from fifteen to seventy-eight years; there were two males to each female; while all occupations were represented, yet it is interesting to note that 32 per cent. of the patients were from farms or rural communities. The average length of time of the period of gastric disturbance was 6.4 years. The shortest time was two weeks (a case of inoperable cancer) and the longest period was more than forty years.

Methods. The emptying power of the stomach was estimated by the administration of a physiological meal of mixed food after the patient had been taken off "diet" and his stomach was, as far as possible empty. Experience taught us that a twelve-hour time interval was of greater diagnostic worth than the four- to six-hour interval as recommended by Riegel and others. The secretory factor was determined by means of the Ewald breakfast of second day bread. This was selected on account of its ease of administration, its lack of disagreeable features, its constancy, and its facility of removal. In the ordinary case the time limit was fifty minutes after administration. Where clinical symptomatology indicated abnormally rapid emptying power the stomach was examined from twenty-five to forty minutes after the test-meal had been given. The size and position of the stomach were determined by inflation through the stomach tube, with the patient recumbent. We used

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an inflation bulb, expelling one and a half ounces of air at each compression. The boundaries of the stomach were determined by the auscultatory method while the inflation was in progress.

In the space allotted for this paper only a brief summary of the work can be attempted. A detailed report is in preparation. It is difficult to present the work without its being merely statistical. A attempt has, however, been made to emphasize the clinical pointings.

SIZE OF STOMACH. The average capacity of the stomach was twenty-seven ounces in females and thirty-three ounces in males where dilatation did not exist. In instances revealing dilatation the average capacity in females was forty-one ounces and fifty-two ounces in males. The greatest gastric capacity was associated with non-malignant, pyloric stenosis.

THE MACROSCOPIC APPEARANCE OF REMOVED GASTRIC EXTRACTS. In addition to evidences of gastric retention this observation was not infrequently of significance.

Color. Traumatic blood was noted in 6.4 per cent. of all cases. Its presence was quite as constant when simple spasm existed at the cardia as when ulceration was present with or without spasm. Its appearance upon lavage had *no consistent relation to any form of gastric disease other than cancer.* Forty-four cases of gastric ulcer had lavage less than forty-eight hours following hemorrhage, and in these cases there was no recurrence of either gross or microscopic bleeding from the maneuver. In the cancer cases (96 per cent. being of the medullary type) traumatic blood on lavage was observed in more than half of the 218 consecutive cases.

Bile Coloring. Various shades of green or yellow were observed in 11 per cent. of the cases in the series. The yellowish shades were the results of straining as a consequence of tubing or occurred in 74 per cent. of the patients who had had a previous gastro-enterostomy (seventy-six). The green coloration from bile was noted quite constantly in cases of gastric atony, ptosis with relaxed pylorus, dilatation with or without ptosis, intermittent pyloric spasm, induration about the pylorus due to ulcer or cancer, and from obstruction below the papilla of Vater. The green shades usually indicated that bile had been present in the stomach for some hours and had become oxidized. In two instances the growth of a chlorophylaceous mould was mistaken for bile before chemical tests or microscopic examination had been made. In 196 instances the presence of much traumatic blood rapidly hid evidences of bile coloring.

Of the cancer cases it is interesting to observe that coffee-colored or dark-brown extracts were noted in but 19 per cent. When such were observed the cases were inoperable. The color of gastric contents was quite as apt to be tan or brownish in partial stenosis with dilatation or atony from non-malignant causes as from cancer.

As will be shown below, however, the odor was a fairly reliable differentiating point between the two conditions. There were 314 cases of achylia gastrica. In 96 per cent. of this group the *dead-white* color of the gastric extract, associated with markedly absent chymification, was a characteristic finding.

Odor. Extracts from normal stomachs have a peculiarly, bland and somewhat sweetish odor. Modifications—quantitative and qualitative—in acidity cause variations. In non-retention cases the sharpness of the sour odor is usually a reliable gauge of the free hydrochloric acid content. In retention cases, high or low free hydrochloric acidity may be masked by the odor from fermentative or putrefactive processes. In 84 per cent. of the cancer group of this series, acrid, rancid odors due to volatile, organic acids were almost pathognomonic. In 76 per cent. of the non-malignant retention class (ulcers, gall-bladder disease, or ptosis with or without atony) the yeasty aroma was almost similarly characteristic. This simply elicited sign proved in our experience to be extremely useful in differential diagnosis. Putrefactive odors are generally due to sloughing of cancer tissue, deterioration of a quantity of blood in the presence of low hydrochloric acidity, fecal contents from obstruction below the duodenum or from perforation of ulcer or cancer into an adjacent viscus.

Amount of Gastric Extract. The average quantity of test-meal removed in the entire series was 108 c.c. The average quantity in the non-retention group was 76 c.c. The average quantity in the retention class was 350 c.c. So-called "hypersecretion" was as frequently observed in pyloric spasm from appendix or gall-bladder disease as from duodenal or gastric ulcer. It is not difficult to mistake partial pyloric stenosis for irritative hypersecretion. But 21 per cent. of the non-stenosing ulcers (duodenal or gastric) exhibited what might be termed hypersecretion. In young adults of both sexes the most common association of hypersecretion was pyloric spasm with diseased appendix or gall-bladder. Some degree of such was constantly present if the symptoms had persisted longer than an average time of 2.8 years.

Mucus. Mucus is a sign of doubtful diagnostic worth. It is more commonly in excess in stenosing cancers or ulcers than when the pyloric channel is free. While 1 per cent. of hyperacidity and hypersecretion cases were associated with pathological increase in mucus, 46 per cent. of the malignant retention group and 29 per cent. of the non-malignant retention class revealed such increase.

Chymification is an index of masticatory thoroughness, of the character of food ingested, of the combining power of hydrochloric acid, of the presence of normal gastric ferments, and of variations in gastric peristalsis and empyting power. The last factor appears to carry the greatest weight in all cases except those of primary or secondary achylia While high hydrochloric acid content gener-

ally assures good chymification, the presence of organic acids and foreign microörganisms (as in gastric cancer) frequently accomplishes similar ends.

The Incidence of Retarded Gastric Emptying Power. This term "emptying power," is especially chosen. "Hypermotility" should be largely limited to what is indicated by "hyperperistalsis." It does not necessarily follow that hyperperistalsis is associated with increased or even normal rate of the stomach's emptying. In fact, our records demonstrate that hyperperistalsis is most commonly found in instances of pyloric spasm or pyloric stenosis that have gastric or extragastric foundation.

Of our entire series, 12 per cent. of the cases showed some grade of retarded gastric emptying power macroscopically. In 8 per cent. of the series this was a *constant* finding. In 4 per cent. it was an intermittant manifestation. In 87 per cent. of the group when gastric retention was a persistant observation, some degree of gastric dilatation was an associated complication. In two out of every three cases where this occurred there was clinical history of delayed vomiting. Some of our most marked instances of gastric dilatation proved to have almost perfect emptying power. Persistent demonstration of gastric retention is an indication for surgical intervention. It denotes mechanical abnormalities or obstruction. In these instances, dilatation of the stomach is a symptom and not the disease. In a given case the degree of gastric retention may vary markedly accordingly as the stenosis is or is not associated with gastric or pyloric spasm. Dilatation of the stomach may likewise vary greatly in degree.

In our series the causes of persistent gastric retention were, in the order of the frequency of their demonstration, gastric cancer, duodenal ulcer, gastric ulcer, cholecystitis with adhesions, gastric atony, tumor of the pancreas, tumor of the liver, hypernephroma, tuberculous peritonitis, and retroperitoneal sarcoma. The causes of intermittent gastric retention were pyloric spasm associated with appendicitis or cholecystitis, gall-stones, duodenitis or gastritis in the presence of increased free hydrochloric acid, and gastroptosis.

In gastric cancer, emptying power was retarded in more than 70 per cent. of instances, irrespective of the location of the growth. In surgical duodenal ulcer, approximately two out of three cases revealed gastric stagnation. In surgical gastric ulcer in rather more than 50 per cent. of instances some grade of retention was proved. Of the pyloric spasms, associated with appendicitis, cholecystitis, gall-stones, or duodenitis, in rather more than 3 per cent. of instances retention was demonstrated. The sign of differential worth in this class of case is that of the variability of the exhibition of retention at different examinations. This sign is of special value to the surgeon who contemplates gastro-enterostomy in such instances. Unless definite obstruction exists at or

near the pylorus the best operative results are only to be expected when artificial stricture is surgically produced. We have the records of the examination of 482 cases of pyloric spasm with intermittent gastric retention, when later the appendix had been removed or operations upon the gall-tract had been performed. In but twenty-one instances was any form of gastric stagnation subsequently demonstrated.

These observations of the incidence of gastric retention, cannot in any way be compared with such information returned from examination by means of the Roentgen ray. It should be urged that, in the method outlined, we are dealing with physiological problems as they occur in a given individual. No one has yet shown that the examinations of gastric function by means of bismuth or barium compounds with the aid of the Roentgen ray is physiological. Consequently, only a long series of observations that have been checked up by surgical procedure or by the subsequent history in medical cases, extending over several years' time, will enable actinologists to formulate statements that will indicate what meaning we can attribute to retention of bismuth or barium in the stomach at the end of, say, a six-hour interval.

The most common causes of increased rate of emptying of the stomach in our series occurred in conjunction with achylia gastrica (primary or associated with severe anemia), vagus hypotonia, temporary or permanent atony without marked gastric dilatation, non-obstructing gastric cancer, colitis, and in numerous nervous states of the young adult.

Gastric Acidity. During the past five years, attempts have been made to belittle the significance of estimations of gastric acidity. This attitude has been brought about largely because of the persistence of surgical teachings. It is expected that those who anticipated that a simple color test would serve in place of clinical cerebration would be doomed to disappointment. While we have been compelled to revise some of our previously held opinions regarding the diagnostic worth of acid estimations of gastric extracts, yet when considered as a part of evidence making for proper conception of disease it would seem that such information can in no wise be neglected. The confusion has arisen chiefly because it was not until recently shown, just what effect upon gastric physiology had extragastric disease. Consequently, the findings in disease extrinsic to the stomach were interpreted, clinically, in the light of known primary gastric ailments.

For the purpose of brevity we would classify our acidity findings under three groups; (1) that comprising recognized disease of the stomach itself; (2) that including lesions of the duodenum, gall-bladder, appendix, and the large bowel; (3) that comprising so-called functional or central disturbances.

Acidities were all estimated by the Toepfer method.

GROUP 1.—ACIDITY IN INTRINSIC GASTRIC DISEASE.

(*a*) Acute gastritis:	
Average—Free HCl	32.0
Total acidity	50.0
Combined acidity	18.0
(*b*) Chronic gastritis:	
Average—Free HCl	42.0
Total acidity	62.0
Combined acidity	14.0
(*c*) Chronic atrophic gastritis:	
Average—Free HCl	12.0
Total acidity	21.0
Combined acidity	9.0
(*d*) Achylia gastrica:	
Average—No free HCl	
Total acidity	8.0
Combined acidity	6.0
(*e*) Gastric ulcer—acute:	
Average—Free HCl	64.0
Total acidity	78.0
Combined acidity	12.0
(*f*) Gastric ulcer with recent hemorrhage:	
Average—Free HCl	35.0
Total acidity	48.0
Combined acidity	13.0
(*g*) Chronic non-retention gastric ulcer:	
Average—Free HCl	42.5
Total acidity	55.0
Combined acidity	13.5
(*h*) Chronic gastric ulcer with retention:	
Average—Free HCl	56.4
Total acidity	74.2
Combined acidity	17.8
(*i*) Chronic perforating ulcer:	
Average—Free HCl	64.1
Total acidity	76.2
Combined acidity	12.0
(*j*) Ulcus carcinomatosum—(64 cases):	
Average—Free HCl	33.4
Total acidity	51.0
Combined acidity	16.0
(*k*) Primary gastric cancer—(122 cases):	
Average—Free HCl	7.46
Total acidity	28.3
Combined acidity	21.0
(*l*) Ulcerating primary gastric cancer (14 cases):	
Average—Free HCl	2.0
Total acidity	34.0
Combined acidity	30.0

SUMMARY. *Group* 1. It is shown that the highest gastric acidities are uniformally determined in acute and subacute perforating ulcer of the stomach; that in simple, chronic gastritis the picture from the stand-point of acidity closely resembles that of ulcus carcinomatosum or of simple gastric ulcer when recent bleeding has occurred, that only 54 per cent. of cases of gastric cancer reveal absent free hydrochloric acid; that in 45 per cent. of instances of gastric cancer the acidity returns may be readily confused with those of simple gastric ulcer, chronic gastritis, or achylia gastrica

unless the figures are rigidly interpreted in the light of clinical history, etc.; that in gastric ulcer with retention there is an increase in both free hydrochloric and total acidity, which fact is in sharp contrast to instances of retention developing in gastric cancer, in which event, as retention comes on, free hydrochloric is progressively lowered, while total acidity simultaneously increases. Other things being equal, in a given case, the diminution of free hydrochloric associated with an increase in total acidity, with the development of obstruction and the demonstration of organic acids, speaks for malignancy.

GROUP 2.—ACIDITY WHERE THE LESIONS ARE MAINLY OUTSIDE THE STOMACH.

(*a*) Duodenitis with pyloric spasm:	
Average—Free HCl	68.0
Total acidity	74.0
Combined acidity	6.0
(*b*) Duodenal ulcer without stenosis:	
Average—Free HCl	59.2
Total acidity	73.0
Combined acidity	14.0
(*c*) Duodenal ulcer with stenosis:	
Average—Free HCl	46.0
Total acidity	84.0
Combined acidity	28.0
(*d*) Cholecystitis, subacute:	
Average—Free HCl	66.0
Total acidity	71.0
Combined acidity	5.0
(*e*) Cholecystitis, chronic:	
Average—Free HCl	32.0
Total acidity	46.0
Combined acidity	14.0
(*f*) Appendicitis, subacute or chronic (usually in young adults both sexes):	
Average—Free HCl	64.0
Total acidity	75.0
Combined acidity	8.0
(*g*) Colitis, subacute or chronic:	
Average—Free HCl	35.0
Total acidity	42.0
Combined acidity	7.0
(*h*) Following gastro-enterostomy for gastric or duodenal ulcer:	
Average reduction in free hydrochlic acid	17.0
Total acidity	32.0
Combined acidity	12.0

SUMMARY. *Group* 2. Of this division the highest free hydrochloric acidities are present in cases of pyloric spasm associated with subacute cholecystitis, appendicitis, and duodenitis. The figures closely resemble those returned in gastric ulcer, as does also the clinical history with the exception of the incidence hemorrhage or chemical proof of bleeding and the time factor. The onset of stenosis in duodenal ulcer increases combined acidity at the expense of the free hydrochloric acidity. After gastro-enterostomy for non-malignant stenosis there is a consistent and noticeable lowering of free hydrochloric and also total acidity, which cannot,

apparently, be wholly explained on the basis of regurgitation of *succus entericus*. In more than three out of four such instances, proof of this having occurred, can, however, be demonstrated by ferment tests or microscopic examination of stained smears.

GROUP 3.—FUNCTIONAL AND CENTRAL DISTURBANCES.

(*a*) In epilepsy of the young adult:	
Average—Free HCl	56.0
Total acidity	62.0
Combined acidity	5.0
(*b*) In neurasthenia, with or without moderate gastroptosis:	
Average—Free HCl	34.0
Total acidity	46.0
Combined acidity	9.0
(*c*) In marked gastroptosis:	
Average—Free HCl	37.0
Total acidity	52.0
Combined acidity	14.0

These figures interpret themselves and require no special comment.

The demonstration of altered or occult blood in gastric extracts by the benzidin or the guaiac tests was possible in 25 per cent. of the cases in the entire series. It was present in 42 per cent. of all retention cases irrespective of the causative lesion. It was demonstrated in 75 per cent. of the 712 cases of gastric cancer. It was almost as frequently shown in duodenal as in gastric ulcer. It would seem that apart from the association of occult blood with malignant processes, its demonstration in gastric extracts has very slight clinical worth.

The Incidence and Significance of Organic Acids in Gastric Extracts. These are rarely demonstrated in non-retention cases, either malignant or non-malignant. In malignant disease, associated with partial stenosis and gastric dilatation, lactic acid was present in 53 per cent. of 712 operatively demonstrated instances. It was rarely demonstrated when free hydrochloric acid rose as high as 10, and in 92 per cent. of cases where lactic acid was found, extensive growths, generally inoperable, were present. Only 3 per cent. of the non-malignant achylias were associated with lactic acid. In but 7 per cent. of the non-malignant retention cases was lactic acid present. It was found in less than 0.5 per cent. of instances of ptosis with atony.

Volatile fatty acids were present in 61 per cent. of the malignant cases and in but 3.2 per cent. of the instances of benign retention or atony. In no instance of non-retention or of simple achylia or hypoacidity were volatile fatty acids demonstrated.

The Significance of the Demonstration of Specific Ferments in Gastric Contents. Space does not permit our going into detail respecting the incidence and diagnostic worth of proving the absence or presence of pepsin and rennin in gastric extracts. It

would seem that proteolysis is closely associated with the presence of free hydrochloric acid, so long as the acid concentration is below 0.4 per cent. and that milk-curdling ferment follows similar laws. In malignancy peptolysis appears to be increased at the expense of proteolysis.

We have made observations upon 827 instances of gastric disease for the detection of specific ereptases in gastric juices,[2] in the hope of recognizing early gastric cancer or malignant ulcer. We have used the formaldehyde titration method as suggested by Sorenson and Schiff. In our experience the average formol titration index in 87 instances of proved gastric cancer was 22.3; the average index in 22 cases of ulcus carcinomatosum was 19.8; the average in 99 cases of duodenal ulcer was 12.4; of 57 cases of simple gastric ulcer 11.6; of 32 cases of benign achylia, 14.1; of 16 instances of pernicious anemia, 14.5; and of 5 cases of cancer of the liver, 4.25. It would appear that in certain instances the estimation of the ereptic power of gastric juice toward peptone solutions is of considerable value when interpreted in the light of clinical history and symptomatology.

We have examined 108 cases for proteolytic ferments by the edestin method, suggested by Fuld and Levison.[3] The results thus far would appear to indicate that early cases of cancer of the stomach, where the free hydrochloric acid is shown to be low show high peptolysis and low proteolysis. In the simple ulcers both peptolysis and proteolysis are low.

We have already mentioned elsewhere our expereince with the demonstration of peptid-splitting ferments in gastric juice, using solutions of glycyltryptophan as the test dipeptid.[4] We made more than 1600 observations. In rather more than 40 per cent. of our proved cases of cancer (186) the reaction was positive. In about 7 per cent. the tryptophan test was positive. Diagnosis of malignant disease of the stomach was in each case quite possible, independent of the chemical test. While gastric abnormalities other than cancer exhibited positive glycyltryptophan reactions, in no class of the disease of the stomach was the test so frequently obtained as in cancer. Low free hydrochloric acid was frequently associated with positive glycyltryptophan tests, and in more than 50 per cent. of these reactions the gastric extracts contained bile or blood or both.

Wolff-Junghans' Test for Soluble Albumin in Gastric Extracts. We have tested 747 gastric extracts where there was low or absent free hydrochloric acid, quantitatively for soluble albumin,[5] according to the method suggested by Wolff of Ewald's clinic. Our work appears to indicate that in cancer this test was a more constant

[2] To be reported shortly.
[3] Biochem. Zeitsch., Bd. vi, Heft 5 u. 6, S. 473.
[4] Smithies, Arch. Int. Med., September, 1912, p. 672.
[5] Smithies, AMER. JOUR. MED. SCI., May, 1914, p. 713

finding than when estimations for presence or absence of hydrochloric acid, of lactic or fatty acids, or of positive glycyltryptophan tests. It was approximately as constant a finding as tests for altered blood and the demonstration of motor inefficiency. It was not so constantly positive as the demonstration of organisms of the Boas-Oppler type or increase in the formol index. In extragastric malignancy and in gastric syphilis the manifestations of the test were inconstant. In the differentiation between malignant and non-malignant achylias the Wolff test, when interpreted in connection with other clinical and laboratory data, proved of considerable value. Positive manifestations were rarely obtained in the achylias of pernicious anemia, simple achylia gastrica and simple achlorhydrias not associated with gastric retention. Simple gastric and duodenal ulcers when accompanied by pyloric stenosis or marked gastric dilatation give confusing responses to the Wolff technique.

Significance of the Microscopic Examination of Gastric Extracts. We have made 6283 microscopic examinations (using the high power) of unfiltered gastric extracts that have been stained by the agar differential staining technique which we devised about three years ago.[6] In brief the summary of our work is as follows:

Starch digestion is not a constant index of the acidity of the stomach juice. Diastatic action of saliva often depends more on motor conditions than upon secretory. The character of the ingested food is a modifying factor. In some instances of low gastric acidity, with normal motility, it would seem that an anti-diastase were present in gastric extracts.

Microscopic remnants of the motor meal have no diagnostic significance other than that indicated when found in association with food macroscopically.

The Diagnostic Significance of the Microörganisms in Gastric Extracts. From our studies we have developed four microscopic pictures which seem almost pathognomonic for certain types of disease. Apart from these we can see nothing very significant. Certainly high gastric acidity by no means insures bacteriologic cleanliness.

Complex 1. *That of benign gastric retention (usually ulcer).* In 89 per cent. of our cases of this type the presence of large numbers of actively budding yeasts, associated with large and small sarcinæ and bacilli, apparently of the colon group, and food bits were demonstrated. The gastric acidity was generally above 50.

Complex 2. *That of gastric cancer.* In 93.8 per cent. of all our proved, late, malignant cases, organisms of the Boas-Oppler group, associated with food retention and acid averaging below 10, was a characteristic picture. In but 30 per cent. of instances were budding

[6] Smithies, Arch. Int. Med., June, 1912, p. 736.

yeasts concomitant. In but 10 per cent. were sarcinæ associated. Threads of streptococci were found in 6.2 per cent. (more commonly in the non-retention group). There is no characteristic microscopic picture of early gastric cancer other than that associated with gastric ulcer of the retention type. In less than 1 per cent. of our cases of gastric cancer were we able to demonstrate so-called "cancer cells" with active mitoses. These were all late cases or cases where the cardiac orifice was involved with a sloughing growth.

Complex 3. *Achylia Gastrica. Primary or Secondary.* In gastric extracts of low or absent hydrochloric acid, when there is atrophy of the mucosa and where motility is not interfered with, there are found long chains of streptococci (resembling beads of a rosary); groups of large, deep-staining cocci, and a peculiar, short, fat, acid-fast rod or cocco-bacillus that grows in short chains or pairs, or alone.

Complex 4. When perforation into an adjacent viscus has taken place in malignant ulcer or primary cancer, or where obstruction has occurred below the duodenum, the picture of immense numbers of thick cocco-bacilli, with or without spirillæ or streptococci, in association with low acidity, retarded food progress and putrefaction, as evidenced by the odor, is shown in more than 94 per cent. of instances.

THE PRESENCE OF CONTINUED HIGH TEMPERATURE IN MALIGNANT TUMORS.

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The presence of continued high fever in malignant tumors is a symptom that has not been sufficiently emphasized by the majority of clinicians. That it does occur in a considerable number of such cases is undoubtedly true, as the study of large series of cases by various authors shows. The purpose of the writer is to report a typical example of continued high temperature in adenocarcinoma of the kidney, with a review of the literature.

The case I wish to report was that of a man, aged forty-four years, who was admitted to Lakeside Hospital, April 19, 1911, complaining of pain in the left side of the abdomen during the preceding four months. The family history was of no importance, except that one sister had died of cancer, and another sister had been operated on several years ago for a fibroid tumor of the uterus which had undergone sarcomatous degeneration. There had been

no recurrence of the sarcoma. The patient had always led a very active life and been in unusually good health.

The present illness dates back about four months, when he began to have a feeling of discomfort in the upper part of the left side of the abdomen. At no time had he suffered from severe pain, but at intervals of a week or ten days he would have a few sharp twinges of pain, which would quickly disappear. Two days before his admission to the hospital he noticed in his left side just below the ribs a prominent mass. His bowels, though always regular, had been constipated during the preceding two weeks and there had been no movement for forty-two hours before coming to the hospital. At no time had there been any jaundice, and the tumor mass must have enlarged rapidly, because he had been examined by several physicians during the two months previously, without anything abnormal being palpated.

Physical Examination. The patient is a large, robust man, showing no cachexia and no apparent loss of weight. Nothing abnormal was found except a prominent bulging in the upper part of the left side of the abdomen. Here, emerging from under the left costal border and extending downward 10 cm., is an elastic smooth swelling, freely movable and descending on respiration. This swelling is not tender to the touch, and gurgling of gas in the colon can be felt between the tumor and the palpating hand. Anteriorly it extends forward almost to the median line and posteriorly well toward the flank. The catheterization of the ureter showed nothing abnormal.

A carbohydrate test meal was given and removed one hour later. The amount obtained was 180 c.c., and consisted of clear fluid with a moderate amount of mucus and food particles. Analysis showed free hydrochloric acid 30, and total acidity 50. There was no lactic acid and the benzidene reaction was negative.

The blood examination showed: red blood corpuscles, 4,964,000; leukocytes, 8800; hemoglobin, 100 per cent. The differential count gave the following result: polymorphonuclears, 74.5 per cent.; small mononuclears, 14.5 per cent.; large mononuclears, 8 per cent.; eosinophiles, 2 per cent.; basophiles, 1 per cent. The red corpuscles stained normally and showed no unusual variation in size and shape. No malarial parasites were found.

On May 5, 1911, the patient was operated by Dr. Crile, an incision to the outer border of the left rectus muscle being made, extending at its upper part to the costal border. On opening the peritoneum the colon presented itself in the wound. This was retracted and a large cyst was found posterior to the mesocolon. The latter was split and the cyst brought into view and aspirated, about six liters of a thin dark liquid being removed. The exact origin of the cyst could not be determined. The walls were sutured to the peritoneum and fascia and drained. Microscopic

examination of sections obtained from the cyst wall showed no evidence of malignancy. The patient made an uneventful recovery from the operation. The urine examination both before and after the operation showed nothing abnormal. Chemical examination of the fluid showed no evidence of pancreatic ferments.

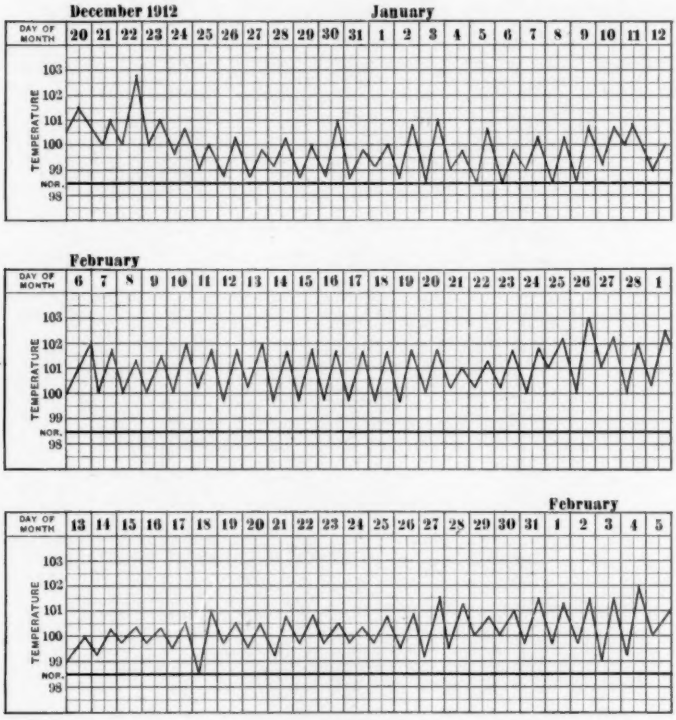
In the succeeding eighteen months the patient remained in very good health. During the first three months he led a very quiet life, but after that he actively engaged in business. He did not have his usual vigor, but his weight remained about the same, 220 pounds. On October 10, 1912, while playing golf he began to feel feverish and dull. His bowels were constipated, but there was no nausea, indigestion, or jaundice. He was relieved somewhat by a cathartic, but for two or three days each week he felt badly. During the next six weeks he lost fourteen pounds in weight and was admitted to the hospital November 23, 1912. At that time there was nothing of any importance found on physical examination except that a large mass could be felt in the upper part of the left side of the abdomen, extending from the costal margin downward to the level of the umbilicus, anteriorly almost to the median line, and posteriorly to the midaxillary line. The mass was somewhat tender, was adherent at the old scar, and gurgling of gas could be felt in the colon as it passed in front of the lower part of the tumor.

On November 24, Dr. Crile again operated, removing a portion of the old scar for diagnosis, which on microscopic examination proved to be an adenocarcinoma. No attempt was made to remove the tumor, as it was thought to be inoperable.

The patient made a good recovery from his operation, and was removed to his home four weeks later. During this time there was no rise in temperature above 99.5°. On December 20 the patient had a nasopharyngitis, with an elevation of temperature varying from 100° in the morning to 102.8° on the afternoon of December 22. During the succeeding six days his temperature varied from 99° in the morning to 100° in the afternoon.

Beginning December 31, 1912, he began to feel chilly about noon, and this was followed by a rise in temperature followed by a profuse sweat. After this the patient would fall asleep about 4 P.M., not awakening for four or five hours. This condition continued daily until his death, May 18, 1913. During the first month his maximum temperature after the chill was 101° during the second month, February, 102°, except the 26, when it reached 103°; during March the maximum temperature varied between 103° and 103.6°, and this condition continued about the same during April. On May 1 his temperature reached 104.4°, and on May 2, 104.2°, but throughout the rest of the month the maximum temperature remained between 103° and 104°. Throughout this period the abdominal tumor remained the same size and

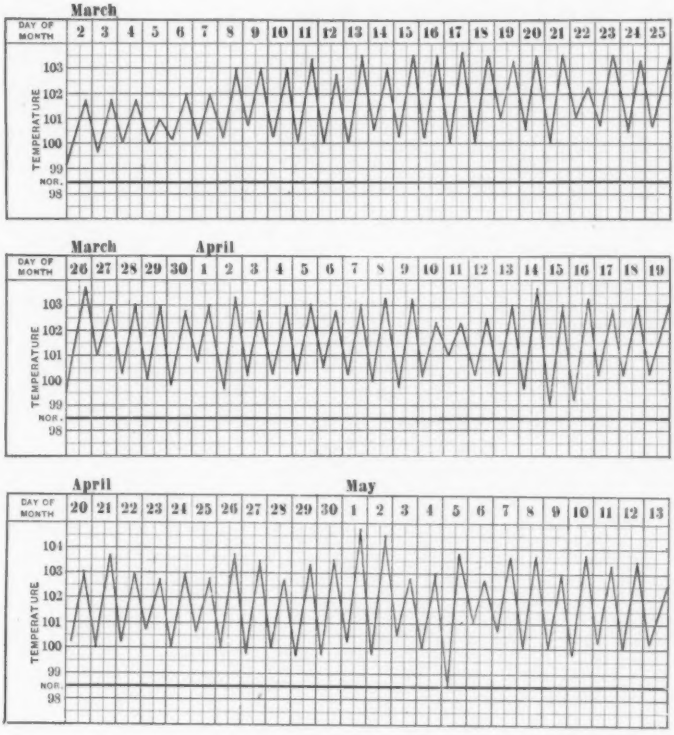
consistency. No evidence of complications could be made out on physical examination. At no time was there more than a moderate leukocytosis, and the blood was repeatedly searched for malarial parasites, but none found; blood cultures were negative. Until April 1 the patient's appetite remained good, and he kept his weight of 195 pounds. After this date he became weaker, lost his appetite, and his weight decreased quite rapidly, though no record



Temperature chart showing continued high fever in a case of adenocarcinoma of the kidney.

was kept, as he could not be weighed, being confined to his bed. The urine was examined twice a week, but showed nothing abnormal beyond a faint trace of albumin during the last two months. Another interesting thing about the case was that there was little tendency to anemia, as the following blood examination will show: February 4: red corpuscles, 5,196,000; hemoglobin (Haldane method), 93 per cent.; leukocytes, 11,200. The differential count

of the stained smear showed small mononuclears, 8.4 per cent.; large mononuclears and transitionals, 7.8 per cent.; polymorphonuclear neutrophiles, 80.4 per cent.; eosinophiles, 3 per cent.; mast cells, 0.4 per cent. The red corpuscles were normal in size, shape, and staining properties. No malarial parasites were seen. Blood cultures and the Widal reaction were negative. February 27: red blood corpuscles, 4,682,000; hemoglobin, 90 per cent.;



Temperature chart showing continued high fever in a case of adenocarcinoma of the kidney.

leukocytes, 14,700. The differential count of the stained smear showed: small mononuclears, 3.7 per cent.; large mononuclears, 2.6 per cent.; transitionals, 2.3 per cent.; polymorphonuclear neutrophiles, 91.3 per cent.; eosinophiles, none; mast cells, none. The red corpuscles were normal in size, shape, and staining properties, and no malarial parasites were seen. There was no growth from the blood cultures, and the Widal reaction was negative.

The patient grew gradually weaker, and died May 18, 1913.

The following is the autopsy report of Professor O. T. Schultz, the postmortem being performed one and a half hours after death:

The body was that of a well-built white male, five feet nine inches tall, weighing approximately 165 pounds. The body was still warm. In the left hypochondrium, about four inches from the median line, was a narrow vertical scar about three and a half inches long, apparently a healed operation incision. A second similar scar of equal length joined this one at its upper end and then extended somewhat obliquely downward and outward. The subcutaneous fat was yellow in color and from one to one and a quarter inches thick. The trunk musculature was of good color and well developed. The pleural, pericardial, and peritoneal cavities were free of excess fluid.

Right lung: The right lung was firmly bound down by old fibrous adhesions. The left lung was everywhere free. The posterior surfaces of both lungs were congested and edematous; otherwise the lungs appeared normal.

Heart: The heart appeared normal in size and consistency. It was not opened or removed.

Abdomen: The stomach was moderately distended, the colon markedly so, with gas. The intestines themselves were everywhere free of adhesions. In the left hypochondrium there were rather easily broken fibrous adhesions between the mesocolon and the anterior abdominal wall. In this region there was a firm, hard mass of tissue extending from the abdominal wall, in the region of the operation wound scars, down deep toward the left kidney region. In the adhesions between the mesocolon and the abdomen was a small mass of tissue made up of cysts measuring 5 to 10 mm. in diameter; these were thin walled and filled with clear fluid. The tail of the pancreas was adherent to the mass of tumor tissue which extended dorsally from the abdominal wall. The pancreas could, however, be readily separated, and when separated showed no involvement. The mesenteric lymph glands were not enlarged. The spleen was about twice its normal size, the free convex surface triangular in shape, with a deep notch in the superior border. The spleen was soft and congested, about half of its substance being occupied by an irregular, triangular, deep red area, whose base was at the capsular surface. Beyond this area the spleen substance was somewhat firmer than normal.

Liver: The margin of the liver came down two fingers' breadth below the costal border on the right side. Upon the inferior surface of the liver, around the region of the hilum, were a number of firm, white nodules measuring from 0.5 to 2 cm. in diameter. In addition, similar whitish areas, softer and more translucent, and varying in size from just barely visible to some 5 mm. in diameter, were scattered in large numbers throughout the liver substance.

Right kidney: The organ showed nothing abnormal except a moderate increase in the thickness of the cortex. The right adrenal was normal.

Left kidney and tumor: The mass of tissue which extended posteriorly from the anterior abdominal wall could be traced directly to the kidney, being attached to the kidney near the pelvis 4 cm. from the lower pole. The kidney could be very readily separated from the posterior abdominal wall and was nowhere adherent except in the anterior middle region mentioned, where the tumor tissue was directly continuous with the kidney. Upon removal, the upper half of the kidney was found to be occupied by a number of cysts measuring from 2 to 7 cm. in diameter. These were thin walled. The contents of some were fluid, dark brown, grumous, apparently made up of broken-down tissue and changed blood. In others the fluid was clearer and contained masses of pale tissue similar to finger-like ingrowths of tissue which extended from the cyst walls into the lumina of the cysts. Still others were almost completely filled with such tissue. The cysts were not adherent externally. At the point of attachment of the mass of tissue which extended from the kidney to the abdominal wall there were a number of firm nodules which had caused some pressure upon the anterior wall of the pelvis of the kidney and had led to moderate dilatation of the pelvis. In the middle region of the kidney, beneath the cystic upper pole, the kidney substance was occupied by a soft, white tissue arranged in rounded nodular areas, from 2 to 10 mm. in diameter. Some of these were opaque and apparently necrotic. The distance from the inferior pole of the kidney to the superior pole of the tumor was 18 cm. The thickness of the tumor in the cystic region was 9 cm. The kidney cortex of the lower pole measured 12 mm. in thickness. From its mesial to its lateral border the tumor measured 12 cm. The posterior surface of the kidney was well outlined and measured 12 cm. from pole to pole; the capsule of the posterior surface stripped readily. The kidney and tumor together weighed 650 grams.

Microscopic Examination. The pancreas is normal. The islands of Langerhans are numerous and well defined. In sections taken from the region where the tail of the pancreas was adherent there is no invasion by tumor tissue.

Spleen: In sections from the dark red middle area the sinuses are widely distended with red blood corpuscles, which are often agglutinated. There is relatively little spleen pulp visible between the distended sinuses; such cells as can be seen still stain well; many of the latter contain finely granular, light yellow pigment. In this region of the spleen the Malpighian bodies are well preserved and stand out prominently in the section. Sections from the more nearly normal appearing spleen tissue show a moderate

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general increase in stroma and endothelial cells; light yellow, granular pigment is present in large amounts.

Left kidney and tumor: In sections from cysts the latter are seen to be filled with markedly branched, papillary ingrowths, which are composed of rather dense central fibrous bands carrying thin-walled bloodvessels; these papillæ are covered with a rather tall cylindrical epithelium. Peripherally such cysts show an invasion of the surrounding stroma by small, oval and circular, tubular alveoli lined by a single layered epithelium whose cells are not quite so tall as those covering the papillæ within the cysts. About some of the cysts the stroma is markedly infiltrated with light yellow, granular blood pigment.

In sections from the solid, whitish nodules present in the kidney the papillomatous character of the tumor is not evident. These nodules are composed of a rather dense fibrous stroma in which are closely placed small tubular alveoli similar to those present about the cysts.

The kidney tissue immediately about the cysts and tumor nodules is compressed, the interstitial tissue markedly increased, the tubules decreased in size, and the glomeruli transformed into dense fibrous bodies. In the cortex of the right kidney and in that of the lower pole of the left kidney the convoluted tubules are prominent, the lining cells larger than normal. There is moderate congestion of the intertubal vessels.

In the mass of denser tissue which extended from the kidney to the abdominal wall there are numerous tubular alveoli separated by narrow bands of fibrous stroma. The papillomatous character present in the cysts is entirely absent here and the tissue has the typical arrangement of a cellular adenocarcinoma.

The small mass of cystic tissue found in the omental adhesions is composed of small cysts, some of which are lined by a single layer of cuboidal epithelium and are filled with finely granular, pink stained material; others are filled with papillomatous ingrowths, exactly like those in the cysts of the kidney itself.

Liver: In the larger tumor nodules the stroma is prominent, more here than in any of the other portions of the tumor; the metastases are of the scirrhus rather than the medullary type. The tumor alveoli are small, round, oval, or irregular in shape, and are lined by an epithelium whose cells vary greatly in size and shape. In the smaller liver nodules the amount of stroma is not so great as in the larger ones; these small metastases begin in the interlobular tissue. The latter is moderately increased in amount even where no invasion by tumor tissue occurred, and is infiltrated with lymphocytes. The peripheral portions of the liver lobules are congested and a moderate amount of fat is present.

Anatomical Diagnosis. Papillary adenocystoma of the left kidney; adenocarcinoma of the left kidney; secondary adeno-

carcinoma of the liver; moderate interlobular hepatitis; recent red infarct of the spleen; hematogenous pigmentation of the spleen; moderate compensatory hypertrophy of the right kidney.

Conclusions. There can be no doubt but that the original tumor was a cyst of the kidney which sprung from the middle region of the organ near the pelvis and pointed directly forward. At this time the tumor was most probably benign, and almost certainly there were present other cysts than the one opened at operation. The tumor began as a benign cystadenoma of the kidney. Beginning thus, continued proliferation of the epithelial lining led to a filling up of the cyst cavities with papillomatous ingrowths; from a benign, pure cystic tumor there developed a papillomatous cystadenoma, a tumor with the potentialities of invasion and malignancy. The invasion of the stroma surrounding the cysts is characterized by a loss of the papillomatous nature and a transformation of the tumor into a typical adenocarcinoma. Many of the new-formed tumor alveoli have the appearance of kidney tubules. With this transformation the tumor became definitely malignant, with the property of spreading by direct invasion of surrounding tissues and of producing metastases. At the time of the second operation the tissue removed for diagnosis from the mass which had replaced the wall of the original cyst was unmistakably carcinomatous, and microscopic examination of some of this same mass of tissue removed at autopsy shows it to have the characters which indicate that it had been growing at a more rapid rate than any other portions of the tumor. In spite of the undoubted malignancy of the tumor, as evidenced by the clinical course of the disease, the invasion of the tissue which replaced the original cyst wall, the multiple metastases in the liver, and the microscopic character of the tumor tissue, the failure of the tumor to grow invasively is its most striking feature. The kidney together with its associated primary tumor was most readily removed at autopsy; there was no invasion of the body wall posteriorly or of the overlying tissue anteriorly. The tumor had grown by direct continuity only anteriorly along the cyst wall, which had been stitched to the abdominal wall at the first operation. Metastases were present only in the liver, and there were most probably a development of the terminal four or five months of life.

The other conditions noted in the anatomical diagnosis are all minor ones, secondary to the tumor itself.

The first author to lay stress on the occurrence of fever in cancer was Wunderlich, who, in 1870, stated that in cancer elevation of temperature is comparatively rare, the temperature being usually normal or subnormal, but at times fever is present in the latter stages. He also mentioned the fact that intermittent fever was occasionally noticed in the early stages of cancer and that

its presence suggested a rapidly fatal course. Kühn, in 1875, reported a case of primary carcinoma of the kidney, accompanied by fever, in a child. In this case, however, the febrile periods were associated with such disturbances as hematuria, gastric distress, and softening of the tumor, which might account for the elevation of the temperature. Brinton is quoted by Leube, in 1876, as authority for the statement that fever is not rare as a symptom of malignant disease. Riegel attributed fever to the complications that occurred during the course of cancer. Nothnagel considered it was a symptom of carcinoma itself; and Kraussold reported two cases of carcinoma of the cecum with all the symptoms of acute perityphlitis. Leichenstern stated that entirely atypical cases occur independent of the stage of the disease. This observation has been confirmed by Osler, Rolleston, Russell, and Finlayson. Additional reports of the association of fever with malignant disease have been made by Hampeln, Hawthorne, Freudweiler, Bull, Marchesini, Badnel, and Eichorst. Puritz and others have recorded the occurrence of fever in cases of sarcoma. A few of the cases so recorded were undoubtedly cases of Hodgkin's disease.

Freudweiler, who has made the most complete study of continued elevation of temperature in malignant disease, reviewing the literature, made a systematic study of 475 case histories in which the diagnosis was made with certainty clinically or anatomically during the years 1884 to 1897. In these cases the organs involved were as follows: stomach 265, pharynx and esophagus 105, liver and gall-bladder 38, the colon and rectum 24, the small intestine, omentum, and peritoneum 3, other organs (including uterus, kidney, and prostate gland) 40. Only those cases with a temperature above 38° C. were considered febrile, because if the cases below this were included with the cases of continuous fever this class would be disproportionately large as compared to the class with intermittent and remittent fever. He made the following classification of his cases according to temperature, excluding all cases in which there were complications or other causes to account for fever: (1) Febris continua—variations of temperature within one degree; (2) febris intermittens et remittens; (3) malaria like fever paroxysms; (4) isolated or short periods of elevation of temperature of less than three days' duration. Of the 475 cases of cancer reported by Freudweiler, 189, or 39.8 per cent. had fever. Of the uncomplicated cases 127, or 24.6 per cent. Thus in cancer of the stomach, 265 cases, 61, or 26 per cent., had fever; cancer of pharynx and esophagus, 105 cases, 22 or 21 per cent., had fever; cancer of liver and gall-bladder, 38 cases, 17, or 45 per cent., had fever; colon and rectum, 24 cases, 7, or 29 per cent., had fever; small intestine, omentum, and peritoneum, 3 cases, 1, or 33 per cent., had fever. Other organs,

40 cases, 9, or 22 per cent. had fever. In the consideration of the four different types of fever he deduced the following facts:

1. Febris continua—cases with a variation of less than 1° C. In this form of fever the duration may be only for a few days or weeks. The temperature may then disappear and return with somewhat different daily variations. The cases with continued fever constituted 1.5 per cent. of total cases and 6 per cent. of febrile cases. It occurred in 6.6 per cent. of cases of cancer of stomach.

2. Eight per cent. of cases of cancer of liver and gall-bladder and 14.3 per cent. of cases of cancer of the colon and rectum.

3. Febris remittens et intermittens (the largest class). Once present this type of temperature usually continues until death. Sometimes the intermittent and remittent types may alternate. This class includes 10.1 per cent. of total cancer cases and 41 per cent. of febrile cases. Its occurrence as to organs was as follows: In cancer of the stomach, 34.4 per cent.; in cancer of the pharynx and esophagus, 39.8 per cent.; in cancer of the liver and gall-bladder, 35.2 per cent.; in cancer of colon and rectum, 46.6 per cent., in cancer of other organs, 66.7 per cent.

4. Cases with malaria-like paroxysms. These cases may have chills and sweats lasting ten to twelve hours and recurring every second or third day. In some of these cases the highest temperature, reaching to 39° or 40°, is present in the morning, and in the afternoon it drops to normal. There were 17 cases of this type of temperature in Freudweiler's 475 cases, or a percentage of 3.6 per cent. or 14.5 per cent. of febrile cases. This author has made three subgroups of these cases: (*a*) Those with sudden onset with chills and sweats, the paroxysms lasting from twelve to twenty-four hours; of this type there were eight cases in his series. (*b*) Those in which the onset was slow with a continuous temperature lasting from two to three days and with slow remission. There were no chills or sweats, and of this type there were four cases. (*c*) Those in which the temperature resembles for a time that seen in group (*a*), and the remainder of the time that of the same character as type (*b*). There were five cases in this group.

5. In this group were included those cases in which there was an occasional elevation of temperature, may be as high as 40° C., and which subsides by lysis. Of the total cases, 9.3 per cent. were of this type, or 38.5 per cent. of the febrile cases.

This grouping of Freudweiler is, of course, more or less arbitrary, but one peculiarity of all febrile cases is noted—namely, the great variations in temperature, which may be considered typical, just as we associate the hectic type of fever with suppuration or tuberculosis.

The question naturally arises, What is the cause of the fever? With our present knowledge of bacteriology, infection can be

excluded in a large percentage of these cases. In one-fourth of Freudweiler's cases there was no ulceration. However, infection may exist without tissue change. In many of these cases the condition is analogous to what we see in Hodgkin's disease, in which three different types of temperature have been described: (*a*) the continuous, (*b*) the intermittent or remittent type, (*c*) the recurrent type. This condition was thought to be a form of sarcoma until within the past few years, and recently the infectious origin seems pretty well established by Bunting and others. Hampeln has pointed out two possibilities of the cause of fever in carcinoma: (1) from the growth itself, and (2) from the growth plus malaria. In my case malaria was excluded by repeated examinations of the blood. It would seem that the most reasonable explanation of the fever is that because of the constant degeneration of tumor tissues, products of autolysis are formed which enter the circulation in small quantities, producing systemic disturbances, such as fever. However, though this seems very probable, no such substances have been isolated nor has their presence been demonstrated.

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THE VASOMOTOR MECHANISM IN PNEUMONIA.

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Clinicians very generally believe that a failure of the peripheral circulation is a frequent cause of death in pneumonia. This belief rests in part on the assumption that the blood-pressure is abnormally low in most persons dying of this disease—an assumption not supported by clear evidence—and, in part, on certain experiments

which seem to show that the vasomotor nervous mechanism is paralyzed in fatal pneumonia. It is my purpose to examine critically this evidence and these earlier observations in the light of investigation made within the past two years.

THE BLOOD-PRESSURE IN PNEUMONIA. *Earlier Statements.* The feeling that a persistently low blood-pressure is of frequent occurrence in this disease is exemplified by statements of the following nature: "The measurement of the blood-pressure will decide often the question of whether we should look to the heart or the blood-vessels to reëstablish the equilibrium of the circulation. Of eleven fatal cases here reported one-half showed vasomotor paralysis and half did not. A knowledge of the blood-pressure in pneumonia will often be of assistance in judging of prognosis and of treatment."[1]

There are, however, a few clinicians who do not concur in this opinion. Weigert,[2] in 1911, reviewed the work of earlier writers on the subject and added a large number of personal observations. He found the data of his predecessors so contradictory that he could draw no conclusions from them. Among his own 38 cases there were 6 deaths. The blood-pressure in these individuals was not low. He separated the recoveries into several groups. In 8 cases there was no effect on the pressure. In 9 cases the blood-pressure curve showed a gradual fall which reached its lowest point, on the average, nine days after the crisis. In 3 cases there were steep falls which bore no relation to the crisis. In the remaining 9 cases the blood-pressure curve rose progressively. Weigert naturally concludes that no rule can be established for the blood-pressure in pneumonia, and that consequently blood-pressure readings are of no prognostic value.

Even though Weigert's evidence is quite conclusive it did not have the effect it should have had, for clinicians continued to believe that low blood-pressures were common in pneumonia. It accordingly seemed advisable to gather further data. Newburgh and Minot collected such data in 1914.

Observations in 1914. Newburgh and Minot[3] postulated that if it be true that grave symptoms and death in pneumonia are due to failure of the vasomotor apparatus, then it ought to be possible to divide persons ill with pneumonia into two groups:

1. A group in which the vasomotor apparatus is intact.

2. A group in which the vasomotor apparatus is seriously injured.

In the first group, blood-pressure measurements ought to form a curve which does not diverge widely from the normal. In the second group the blood-pressure ought to be low in proportion to the

[1] A. Lambert, Blood-pressure in Pneumonia, Jour. Amer. Med. Assoc., 1911, lvii, 1827.

[2] Ueber das Verhalten des arterillen Blutdrucks bei acuten Infectionskrankheiten, Vollkmann's kl. Vortrage, 459.

[3] The Blood-pressure in Pneumonia, Arch. Int. Med., 1914, xiv, 48.

gravity of the symptoms, and it should be very low indeed as death approaches.

In order to decide the question, Newburgh and Minot compared the course of the systolic pressure in 19 fatal cases with the pressure in 26 cases which recovered. The resultant curves[4] clearly showed that the systolic pressure in the fatal cases were continuously above the systolic pressure of the persons who recovered.

It appears from the above that persistently low blood-pressures are not of common occurrence in individuals dying of pneumonia. Consequently, failure of the peripheral circulation cannot be a common cause of death in pneumonia.

THE STATE OF THE VASOMOTOR CENTRE. It might seem logically superfluous to discuss the state of the vasomotor centre in pneumonia after demonstrating that the blood-pressure is not abnormally low, since if the vasomotor nervous mechanism were seriously impaired the blood-pressure would of necessity be low. So important, however, is the condition of the vasomotor apparatus in the prognosis and treatment of pneumonia that additional proof of its normal state cannot be unwelcome. Not less important is the examination of the state of the vasomotor arcs concerned in maintaining the normal reflexes by which peripheral stimuli may vary the blood-pressure and thus increase or diminish the blood supply to the lungs and other vascular areas. It is particularly desirable that this evidence be supplied by experiments on animals. Evidence will now be furnished that the vasomotor centre and its afferent and efferent nerves are normal in pneumonia.

The Negative Observations of Romberg. Romberg and his associates[5] attempted such experiments in 1899. In order to test the state of the vasomotor mechanism they made use of the fact that certain stimuli arising in the skin and mucous membranes call forth reflex activity of the vasomotor cells in the blulb. Impulses originating in these cells cause constriction of the small arteries with consequent elevation of blood-pressure. Absence of this reflex is evidence of physiological failure of a portion or the whole of the arc over which the impulses travel, provided experimental errors are excluded.

Romberg and his associates produced a fatal pneumococcus septicemia in rabbits by inoculating virulent cultures of the organism, and then examined the state of the vasomotor reflex in various stages of the disease by observing the effect on the carotid blood-pressure of electrical stimuli applied to the anal and nasal mucous membranes.

[4] The curves in reference will be found in the communication by Newburgh and Minot, loc. cit.

[5] Romberg, Pässler, Bruhns, Müller, Experimentelle Untersuchungen über die allgemeine Pathologie der Kreislaufstörung bei acuten Infectionskrankheiten, Arch. f. klin. Med., 1899, lxiv, 652.

In the early stages of the disease sensory stimuli always caused a marked elevation of blood-pressure. At a later period, when the appearance of the animals suggested the approach of death and the temperature was falling, the reflexes were still present but did not attain the normal height. Finally, when the animal was in a state of collapse and death was imminent no rise of blood-pressure followed peripheral stimulation. As a result of their observations, Romberg and his co-workers believed that they had proved that death in acute infectious diseases was the direct outcome of paralysis of the vasomotor centre in the medulla.

These experiments had a great effect on clinical opinion. Physicians on both continents accepted the new theory without qualifications and began to direct their chief therapeutic efforts in pneumonia against the ever-threatening or already existing vasomotor paralysis. Hence the almost universal administration of strychnin, caffein, camphor, adrenalin, and salt solution in this disease.

But it is to be observed that the evidence upon which this hypothesis is based is of the negative sort. It rests entirely upon a failure to obtain certain physiological responses. It is accordingly exposed to the vital defect inherent in all negative evidence. Such negative testimony is valuable only when positive evidence is lacking.

Positive Observations. Porter and Newburgh[6] have recently completed experiments on animals from which they obtained positive information regarding this problem. They produced not only pneumococcic septicemia in rabbits, but also acute fatal pneumonia in rabbits, cats, and dogs. In order to judge of the condition of the vasomotor apparatus, they measured the vasomotor reflex. But instead of using precarious reflexes from the mucous membranes, Porter and Newburgh exposed and cut the depressor and the sciatic nerves and stimulated the central ends.

Several reasons make blood-pressure data obtained from stimulation of the depressor nerve specially valuable. Since the depressor nerve is composed entirely of fibers which are afferent to the vasomotor centre, impulses pass directly over this nerve to the centre. Other nerves contain fibers of widely different function. In many cases impulses must first pass through the spinal cord where the vasomotor fibers may be exposed to influences not present in the case of the depressor nerve. The chance of error is increased when the stimulating current is applied to the unbroken skin or mucous membrane instead of directly to a nerve trunk. The depressor reflex may be measured in the absence of curare. The latter, unless given with the greatest care, may interfere seriously with the work of the heart and may cause a large fall of blood-pressure. Even under the best conditions, vasomotor reflexes are often absent for

[6] The State of the Vasomotor Apparatus in Pneumonia, Amer. Jour. Physiol., 1914, xxxv, No. 1.

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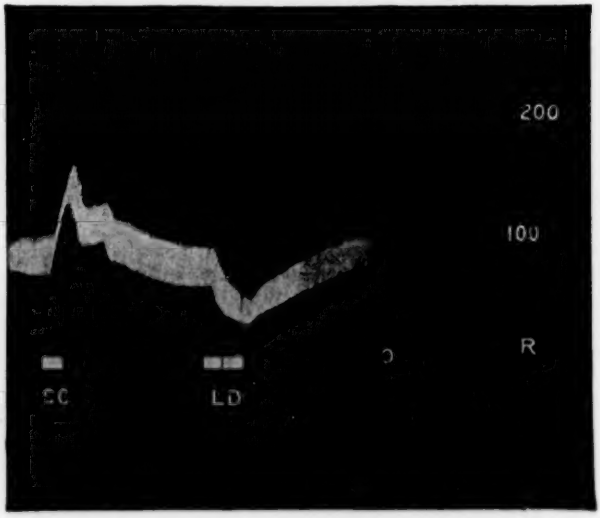

FIG. 2.—Showing the effect of stimulation of the sciatic and of the depressor nerve in a cat near death from pneumonia. (Reprinted from the Amer. Jour. Physiol., 1914, xxxv, No. 1.)

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March 18, 9.30 A.M. The temperature was 34° C. The respiration was markedly labored and of the type seen in laryngeal stenosis. The animal was relaxed and lying prone and seemed at the point of death. It was immediately placed on the operating board and given a few whiffs of ether.

At 10 A.M. both vagi were cut.

At 10.45 A.M. 1 c.c. of curare was cautiously given. Stimulation of the central end of the left vagus at 11.10 A.M. caused the pressure to fall from 80 to 46 mm. Hg. (Fig. 1).

At 11.55 A.M. stimulation of the sciatic raised the pressure from 45 to 65 mm. (45 per cent.). The animal was now killed.

Autopsy. The total lung area, except the tip of the left upper lobe and the extreme edge of two other lobes, was mottled, gray red, firm, non-crepitant, and voluminous. The cut surface, also gray red, was moist and exuded seropus. Scattered through the lung were may areas of hemorrhage and necrosis. The liver contained very many small foci of hemorrhage. The spleen was large and soft. The pericardium and endocardium showed several small areas of hemorrhage.

These experiments prove that the vasomotor centre was not impaired in any of the examples of fatal pneumonia studied.

SUMMARY. It has been pointed out that there are two main arguments offered in support of the hypothesis that the peripheral circulation is paralyzed in pneumonia. The first argument is based on the assumption that the blood-pressure is abnormally low in fatal pneumonia. It has been shown that this assumption is incorrect. The second argument is that the vasomotor reflexes are absent in fatal pneumococcus septicemia. This has been disproved by positive data showing that the vasomotor reflexes are normal in fatal pneumonia.

The conclusion that the vasomotor apparatus is not impaired in pneumonia is fully warranted.

[1] Loc. cit.

gravity of the symptoms, and it should be very low indeed as death approaches.

In order to decide the question, Newburgh and Minot compared the course of the systolic pressure in 19 fatal cases with the pressure in 26 cases which recovered. The resultant curves[4] clearly showed that the systolic pressure in the fatal cases were continuously above the systolic pressure of the persons who recovered.

It appears from the above that persistently low blood-pressures are not of common occurrence in individuals dying of pneumonia. Consequently, failure of the peripheral circulation cannot be a common cause of death in pneumonia.

THE STATE OF THE VASOMOTOR CENTRE. It might seem logically superfluous to discuss the state of the vasomotor centre in pneumonia after demonstrating that the blood-pressure is not abnormally low, since if the vasomotor nervous mechanism were seriously impaired the blood-pressure would of necessity be low. So important, however, is the condition of the vasomotor apparatus in the prognosis and treatment of pneumonia that additional proof of its normal state cannot be unwelcome. Not less important is the examination of the state of the vasomotor arcs concerned in maintaining the normal reflexes by which peripheral stimuli may vary the blood-pressure and thus increase or diminish the blood supply to the lungs and other vascular areas. It is particularly desirable that this evidence be supplied by experiments on animals. Evidence will now be furnished that the vasomotor centre and its afferent and efferent nerves are normal in pneumonia.

The Negative Observations of Romberg. Romberg and his associates[5] attempted such experiments in 1899. In order to test the state of the vasomotor mechanism they made use of the fact that certain stimuli arising in the skin and mucous membranes call forth reflex activity of the vasomotor cells in the blulb. Impulses originating in these cells cause constriction of the small arteries with consequent elevation of blood-pressure. Absence of this reflex is evidence of physiological failure of a portion or the whole of the arc over which the impulses travel, provided experimental errors are excluded.

Romberg and his associates produced a fatal pneumococcus septicemia in rabbits by inoculating virulent cultures of the organism, and then examined the state of the vasomotor reflex in various stages of the disease by observing the effect on the carotid blood-pressure of electrical stimuli applied to the anal and nasal mucous membranes.

[4] The curves in reference will be found in the communication by Newburgh and Minot, loc. cit.

[5] Romberg, Pässler, Bruhns, Müller, Experimentelle Untersuchungen über die allgemeine Pathologie der Kreislaufstörung bei acuten Infectionskrankheiten, Arch. f. klin. Med., 1899, lxiv, 652.

In the early stages of the disease sensory stimuli always caused a marked elevation of blood-pressure. At a later period, when the appearance of the animals suggested the approach of death and the temperature was falling, the reflexes were still present but did not attain the normal height. Finally, when the animal was in a state of collapse and death was imminent no rise of blood-pressure followed peripheral stimulation. As a result of their observations, Romberg and his co-workers believed that they had proved that death in acute infectious diseases was the direct outcome of paralysis of the vasomotor centre in the medulla.

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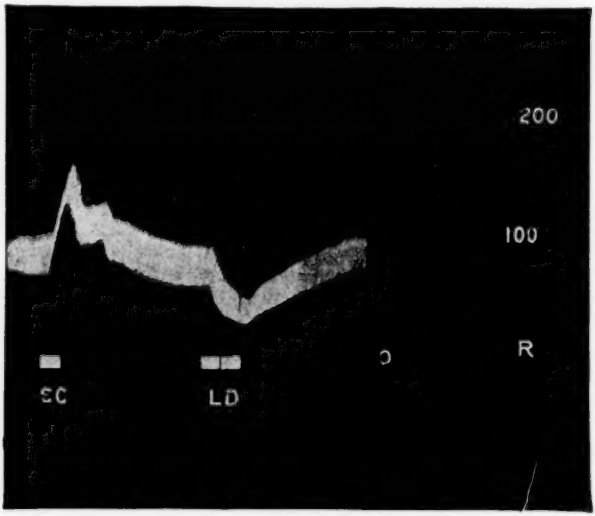

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CONCERNING VASOMOTOR AND TROPHIC DISTURBANCES OF THE UPPER EXTREMITIES; WITH PARTICULAR REFERENCE TO THROMBO-ANGIITIS OBLITERANS.

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It is not generally known to clinicians that certain well-recognized vasomotor and trophic disturbances of the extremities may, on the one hand, be the clinical manifestations of occluded vessels, and may also, on the other hand, be associated with arteries and veins that are organically intact. To the latter group belong those interesting symptom complexes which have been described under the name Raynaud's disease, erythromelalgia and acroparesthesia, multiple neurotic gangrene, scleroderma, sclerodactyly, and chronic acro-asphyxia. Considerable attention has been focussed upon these conditions, and attempts have been made to differentiate various discrete syndromes under the above-mentioned appellations. It is conceded that all have one feature in common, *that the arteries and veins have suffered no organic alteration in their patency.* Comparatively little, however, has been written to show that there is a distinct clinical and pathological entity, *thrombo-angiitis obliterans*, with which there may be associated clinical manifestations almost identical with those that belong to these other diseases. It is of no little importance to be aware of this fact and to be able to recognize that there is a disease whose symptoms depend upon vascular occlusion, for the prognosis and treatment of the two types of affections are in no way identical.

A clinical study of 200 cases of thrombo-angiitis obliterans during the last eight years (1906 to 1914) has enabled me to watch the course of this remarkable disease through all its clinical stages. Many of the cases have been followed from five to eight years, and the presence of interesting mutations in the symptomatology could be recorded. It was found that in a certain number of the patients the upper extremities are involved, although it is usually believed that only the lower extremities are affected. And particularly here were patients' histories encountered that singularly emphasized the unreliability of clinical signs alone in diagnosis. Furthermore, as shall be shown in some instances, thrombo-angiitis may, by virtue of the predominance of certain objective phenomena, masquerade as almost any of the true vasomotor and trophic diseases. Yet a careful study of each and every case will almost always make possible the recognition of the nature of the morbid process.

It may be of some clinical interest, therefore, to present here (1) the most striking examples of the various forms in which the disease may affect the upper extremities, where thrombo-angiitis obliterans is most frequently mistaken for other affections, and (2) to point out upon what features the diagnosis of the malady may be made.

A survery of the histories shows that the upper extremities may be clinically involved in the following ways: (1) without subjective symptoms; (2) with vasomotor symptoms predominating; (3) with trophic disturbances alone; (4) with gangrene of slight extent; (5) with extensive gangrene threatening the viability of the extremity; (6) with extensive atrophy of the hand and forearm; and (7) with changes simulating scleroderma and sclerodactyly.

I. Thrombo-angiitis Obliterans of the Upper Extremities Without Symptoms. Just as in thrombo-angiitis of the lower extremities, there are cases in which the radial or ulnar artery, or both, become gradually closed without the patient's experiencing any noticeable symptoms. In some instances, absence of pulsation was discovered during a routine physical examination; in others, where symptoms were present in the lower extremities, investigation of the radial and ulnar vessels had demonstrated their occlusion.

Case I.—J. A., male, aged forty years, Russian, began to have trouble in the right leg ten years ago (1904), pain coming on during walking, subsiding when at rest. Gangrene of the little and of the big toes developed, leading to amputation of the leg at its middle in 1906. Since 1908, similar symptoms involved the left leg, and the first and second toes became ulcerated, also requiring amputation. During the period of clinical observation the right radial pulse gradually disappeared, although no vasomotor or trophic manifestations could be elicited on examination. The patient was lost sight of so that the further course could not be followed.

The symptoms of Raynaud's disease, too, may be closely mimicked, as in the following cases:

II. Cases in which Vasomotor Phenomena Preponderate. Such an instance is described in the following history, where, after about ten years of migrating phlebitis, and the usual circulatory disturbances of the lower extremities, distinct evidences of involvement of the vessels of the arm and hand supervened.

Case II.—A. B., male, aged thirty-one years, Russian, noticed the appearance of small hard lumps under and in the skin of the calf of both legs in 1904 (ten years ago). They were painful, lasted for a few days or a week or more, and would then disappear (migrating phlebitis). For three years similar lumps and strands would come and go over the lower and inner side of the right thigh. About seven years ago he began to experience cramp-like pain in the right foot and calf of the leg on walking. Later the right

foot became "cold." An ulcer developed on the third toe and showed no tendency to heal.

For seven years he has been suffering with similar symptoms in both legs and feet, the typical symptoms of pulseless vessels, erythromelia, ischemia in the elevated position, and gangrene of several toes being present. He now (1914) has already lost four toes of the left foot and two of the right.

Four months ago his right hand began to trouble him. In cold weather it would become very pale, particularly the little finger. On warming the hand, color would gradually return. Of late, however, the tip of the little finger has been bluish for days at a time, although excessive heat seems to bring back a normal color.

Physical Examination, May 6, 1914. The radial and ulnar arteries of both sides pulsate distinctly. Both hands perspire profusely, and are somewhat cold. The tip of the little finger of the right hand is cyanotic and deeply discolored over its palmar aspect. Pressure over this part elicits some pain. Roentgen-ray examination of the hand is negative.

On July 31, 1914, patient says that the little finger and thumb of the right hand feel cold. Scales form on the tip of the little finger, and when these separate, leave a healed depression. He has no pain.

Physical examination shows that both the little finger and the thumb are distinctly cold to the touch, the coldness extending to the base of the fingers. The other hand and fingers are warm. The radial and ulnar arteries pulsate well. On elevation there is no appreciable change in the color of the fingers.

In short we have here an example of thrombo-angiitis in which vasomotor symptoms initiate the onset of the disease in the upper extremities. Previous experience warrants the assumption that we may either expect a complete cessation of the symptoms in the hands, if adequate collaterals be established, or progressive occlusion of vessels until the radial and ulnar arteries become obliterated or until gangrene ensues.

Case III.—J. V., male, aged thirty-four years, Russian, admitted to the Mt. Sinai Hospital (Dr. Lustgarten's service) December 17, 1907, says that three and a half years previously he noticed that his fingers were cold but not blue. The following winter the same symptoms returned, but, in addition, the skin of the tip of the right middle finger became dry and a "wound" spontaneously developed. For the past two years his hands would get blue, cold, and numb on exposure to cold, their natural color returning in a warm room. There was never any pallor. A sort of "sticking" pain in the finger tips would regularly accompany the state of blueness.

Physical Examination, December 17, 1907. Both hands are deeply cyanotic up to the wrist, and very cold. During the examina-

tion bright-red or crimson-colored spots can be seen to appear in the dorsum and palm. Over the back of the hand these red blotches become very distinct and do not shade off into the blue areas. The two distal phalanges remain deep blue. If the hands be observed for a still longer time (five minutes) the red color becomes paler and is mottled with a yellowish-pink; at times a totally different and much lighter shade, variegated with red and blue, will completely replace the deep colors first noted. In the palm the red areas are not so apparent, but they also give way at times to the lighter shades. The terminal phalanges of the ring fingers are enlarged, those of the middle fingers somewhat less so. When the hands are held above the head for two or more minutes the redness disappears, a pale sickly purple remaining. The radials and brachials pulsate well.

In the lower extremity a similar picture is present, but there are evidences of obliteration of the vessels. The right dorsalis pedis cannot be felt, although palpated on many occasions from December 17, 1907, to January 20, 1908. In the left dorsalis pedis there is fair pulsation. There is ischemia in the elevated position of the legs, as evidence of the impaired vascular supply, and bespeaking the presence of the lesion, thrombo-angiitis.

If such an exquisite example of vasomotor disturbance can belong to a case of thrombo-angiitis obliterans, there is little wonder that confusion should exist in the differentiation of the symptoms due to neurogenous and organic lesions of the vessels. What the distinguishing points are upon which the diagnosis must be based will be discussed later in the paper.

III. Cases with Trophic Disorders Only. In some patients, distinctive signs of an affection of the upper extremities manifest themselves as trophic disturbances not extensive enough to lead to gangrene. The disease may be wholly overlooked by the patient and, when the lesion has healed, it may be subsequently referred to by him as a slight "sore" or "ulcer" developing without cause. Were it not for the presence of the disease in the lower extremities and for the changes in the radial pulse the nature of the trophic disorders would be difficult of solution.

Case IV.—T. S., aged thirty-one years, Russian, consulted me in May, 1914, because of the condition of his left foot. Three and a half years previously he experienced pain in the sole of the left foot on walking and was treated for rheumatism. Two years after the onset a sore developed between the fourth and fifth toes of the left foot and another one on the tip of the big toe of the left foot. Since then the foot became red and the little toe gangrenous, falling off about a year ago. About this time his right leg began to trouble him, the symptoms being pain in the calf on walking.

Two and a half months ago there developed a spontaneous ulcer over the middle phalanx of the right hand, not accompanied

by any evidence of inflammation, hardly painful, and not brought about by any injury. . He was treated for this for about eight weeks, when the wound healed.

Physical Examination, May, 1914. Over the middle phalanx of the right hand there is an irregularly shaped scar, about 8 mm. in length and 4 mm. in width, evidently the site of the old healed lesion. The right radial pulse is not perceptible.

We have here a typical case of thrombo-angiitis of the lower extremities, first involving the left then the right lower extremity, and three years later manifesting itself also in the hand, with trophic disturbances and obliteration of the radial artery.

IV. Cases with Gangrene of Slight Extent. Not a small number of the patients that suffer with occlusion of the vessels of the upper extremities come to us with a history of having had pain in the tip of one of the fingers for a considerable time. This is followed by a change in the color of the skin, usually reddening of the tip of the fingers, as if it were inflamed. Later there develops a sore or the skin changes color and becomes gangrenous, usually at the tip of a finger, although the lateral margin of the finger may be first affected. The following three cases are examples of this group:

Case V.—L. B., aged forty-eight years, Russian, male, admitted to Mt. Sinai Hospital (Dr. Lilienthal's service), May 1, 1910, says that his left leg was amputated below the knee some ten years ago. Six years later he lost his right leg in the same way. Now for six months the index finger of the left hand has been painful and red at the tip; this has since improved. Four months ago the index finger of the right hand also became red and painful, and during the last three weeks the greater part of the last phalanx has become mortified.

Physical examination shows an old scar at the tip of the left index finger and poor radial and brachial pulse. The terminal phalanx of the right index finger is completely exposed, the dry bone presenting. On elevation of the right hand, marked ischemia occurs.

The right radial pulse is absent, the brachial only faintly pulsating. The gangrenous process is evidently progressing, since a portion of the second phalanx is already involved.

Case VI.—D. B., aged thirty-five years, male, Russian, first examined by me on July 16, 1904, at Mt. Sinai Hospital. He had been treated in the hospital eight years previously for "phlebitis" of the right leg. A portion (five inches) of a large vein was diseased at that time, the history recording that the process was "migrating," moving up and down the thigh. He says that this trouble lasted off and on for two years. In 1903 there were "lumps" in and under the skin of the righ leg and then three months later in the left leg. Such swellings would last a week, develop into

hard, "tender spots," with a covering of red skin, and on one occasion three such spots appeared on the left arm in front of and just below the elbow.

Physical Examination, July, 1904. In the left antecubital region there is a thickened, slightly reddened cord about two inches long. Another is situated on the ulnar aspect of the same forearm near the elbow. The right forearm presents a similar vein about three inches from the elbow; the skin is not reddened. On the inner side of the right cubital space a subcutaneous, adherent nodule can be felt; it is very tender. There are several such nodules in the right calf and smaller ones over the left shin bone. No edema, but slight cyanosis of both legs in the pendent position. A portion of one of the thrombosed arm veins was extirpated for study.

Course. A year later (1905) symptoms referable to an affection of the deep vessels of the left lower extremity manifested themselves, namely, coldness and blueness of the left foot and superficial ulcers on the toes. In February, 1907, he developed a gangrenous patch at the tip of the middle finger of the right hand. His doctor had been treating him for a "felon" of the middle finger of the right hand. His hand had been cold for several weeks and the middle finger painful. Four weeks previously a black, "dead" spot appeared at the tip of the finger, and since then, what with cutting it and self-treatment, he thought that the present intensely painful affection had overtaken him.

Physical Examination, February 1, 1907. A portion of the tip of the middle finger is gangrenous; there is no infection; the distal phalanx seems to take part in the process of mortification.

On holding both hands above the head for some time the right becomes appreciably more ischemic than the left; it does not attain the cadaveric hue characteristic of the lower extremities, but becomes markedly pale, a bluish-red tinge remaining in the distal phalanges. The pain is not increased in this portion. In the dependent position the color rapidly deepens in the left hand, soon assuming a reddish-blue hue, the fingers being particularly discolored. Both radial pulses are felt, the left somewhat small. On the dorsum of the hand, just over one of these veins, there is a bean-sized, indurated area; the skin over it is adherent and tender. About one inch above the wrist, behind the radius, there is a reddened, hard cord more than an inch in length (doubtless a thrombosed vein). The finger improves very slowly.

Here there is most beautifully illustrated that group of cases in which a long period of "migrating phlebitis," first of the lower and then of the upper extremities, dominates the clinical picture. Then, when the signs of impaired circulation of the legs have become well established, the hands, too, show unequivocal marks of the closure of small distal arteries, in the form of small areas of gangrene.

CASE VII.—M. S., aged forty-seven years, Russian, was admitted to Mt. Sinai Hospital on June 25, 1907, giving the following history: About eight or nine months ago he noticed that the fourth toe of the left foot was cold, blue, and painful. About four months ago the pain became so severe that he consulted a physician, who told him that an infection had taken place. Since this time a sore developed under the nail and the nail bed became black.

FIG. 1.—Trophic changes in index finger of Case VII.

Physical examination showed complete gangrene of the distal half of the fourth toe of the left foot, absence of pulsation in the dorsalis pedis artery, an area of superficial gangrene of the skin on dorsum of the foot, intense erythromelia (hyperemia of the foot) in the dependent position, and marked ischemia in the elevated position. June 28, 1907, amputation was done by Dr. J. Wiener through the tarsometatarsal articulation. On July 5, re-amputation was done through the middle third of the leg, the wound healing slowly.

In 1910 the disease began to involve the right leg in the same typical manner, leading also to dry gangrene of the fourth toe. When examined in March the popliteal, posterior, tibial, and dorsalis pedis of the right leg could not be felt.

In short we have a typical case of thrombo-angiitis obliterans,

first involving the left lower extremity leading to gangrene, amputation, and some three years later involving the right leg.

In March, 1914, I again saw the patient, who now complains of symptoms in the left hand.

March 18, 1914. For several months he has had pain in the tip of the left index finger and lately the finger has changed color, becoming withered and glossy.

Physical examination shows an ulcer at the tip of the left index finger, the live skin above it atrophied and glossy, the hand somewhat smaller than the other, and the fourth finger of the same hand distinctly shrunken. The radial pulse of this hand cannot be felt (Fig. 1).

We are evidently dealing here with a case in which some seven years after the onset of the disease in the lower extremities the left upper extremity became attacked, as evidenced by ulceration and trophic disturbances.

An interesting group is formed by those patients in whom trophic disturbances and gangrene are the salient features. These are the cases so often confused with Raynaud's disease. In our experience the lower extremities are regularly involved at some time or other, and it is, therefore, necessary to watch carefully for the advent of the typical symptoms in these, so that a correct interpretation of the phenomena in the fingers and hands may be made. The following two histories will well illustrate the cases in which:

V. Extensive Gangrene Threatens the Viability of the Extremity. Case VIII.—A. K., male, aged twenty-seven years, Russian, was admitted to Mt. Sinai Hospital January 4, 1908. About two years previously he had had severe pain in the middle finger of the right hand. The finger became cold, at times very blue, and extremely painful. These symptoms persisted for about two months, when he was told to have the nail removed. Shortly after this was done the tip of the finger became dry and black. After several months the terminal phalanx separated spontaneously, but a wound remained which refused to heal.

For about two months his left hand has been affected, there being excruciating pain in the left middle finger of the left hand, and the fourth finger of the right hand also being somewhat painful for two months. He thinks that the tip of the middle finger of the left hand first became dark blue or purple, and lately has become dry and black.

Physical Examination, January 4, 1906, shows that the distal phalanx of the middle finger of the right hand is absent, the tip of the fourth finger showing a small patch of dry gangrene of the left hand; there is beginning gangrene of the distal phalanx of the middle finger.

Somewhat more than a year later, February 24, 1907, he was again admitted to the hospital, presenting evidences of thrombo-

angiitis of the left foot. The second toe of the left foot had been ulcerated for about three months, and gradually all the toes of that foot, except the fourth, became involved in the same process.

Physical Examination, February 24, 1907. Left foot: On the dorsal and plantar surfaces of the great toe there are ulcers. A similar condition is found at the tip of the second toe and on the plantar and dorsal surfaces of the fifth toe. The skin about the ulcer is sloughing and shows no tendency to heal.

The right foot is negative. The right hand shows an absence of the terminal phalanx of the third finger. Both hands are cyanosed.

March 22. Amputation of the toe. Wound does not heal.

May 17. Re-amputation through the leg, by Dr. C. Elsberg.

Physical Examination, May 20, 1907. The left radial pulse is absent and the artery appears to be converted into a hard cord. In the right radial artery a very faint pulse is perceptible. The brachial artery seems to be much thickened, although the pulsation is good. Ever since amputation of the left leg was done, the stump was painful, discolored, bluish, presenting a wound that failed to heal. Finally, on January 2, 1909, the patient consented to re-amputation. I performed the Gritti-Stokes amputation, the stump healing kindly.

January 3, 1909. The tip of the little finger of the right hand presented a small spot of gangrene about 1 cm. in diameter. The distal phalanx of the little finger is absent. The nail of the fourth finger is deformed and thickened. In the dependent position the fingers become cyanotic, with a slight increase in the normal red color. The left hand is normal as regards color, but the nail of the middle finger as well as the tip of the finger are very much deformed.

The right radial artery is felt as a cord, and no pulse can be detected; the ulnar artery is also pulseless; the brachial pulse is poor. The left radial artery is faint, the ulnar cannot be felt, the brachial also is poor. In the elevated position the right hand becomes somewhat paler than the left, but neither becomes very much blanched.

Lower extremity: The stump is in good condition. The right foot shows evidences of development of thrombo-angiitis, the dorsalis pedis and posterior tibial arteries being absent, and there are other evidences of involvement of that leg.

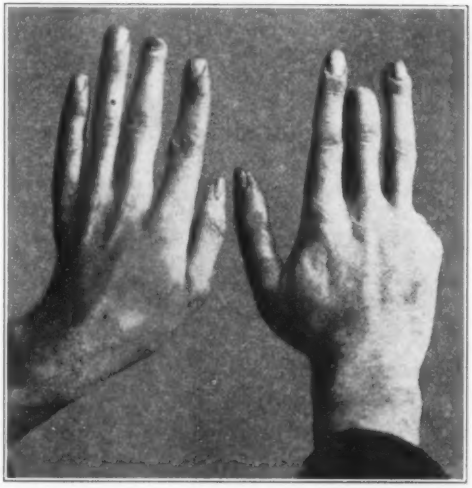
December 30. The fifth finger of the right hand presents an ulcer at the tip, the result of the separation of a gangrenous patch. He says that he has had pain in that finger for about three months, and that gangrene set in about three weeks ago.

February, 1910. The trophic disturbances, involving the little finger of the right hand seem to be progressive. The tip of the finger shows advancing gangrene, the rest of the finger is swollen and red. In the dependent position the third and fourth fingers

become intensely red and slightly cyanotic. Left hand: Here there has been no progression of the symptoms.

FIG. 2

FIG. 3



FIGS. 2 and 3.—Hands in Case VIII, results of gangrene and amputation.

February 2, 1910. The little finger of the right hand was amputated (Figs. 2 and 3).

This is a good illustration of those cases of thrombo-angiitis obliterans in which the symptoms first make their appearance in the upper extremities, are initiated by pain, and followed by trophic disturbances and gangrene. In this case the terminal phalanx of the middle finger and the whole of the little finger of the right hand were lost. During the evolution of these symptoms the disease attacked the left leg, where even greater progress was made than in the upper extremities, amputation being the outcome. Pathological examination of the vessels of the amputated left limb showed the usual lesions of thrombo-angiitis obliterans.

Case IX.—S. A., male, Russian, examined March 23, 1905, gives a typical history of thrombo-angiitis obliterans of the left lower extremity, finally leading to gangrene, for which the leg was amputated August, 1903, and re-amputated September 5, 1903, at the knee.

Fig. 4.—Amputated arm of Case IX. (Photograph taken from specimen after preservation in fixative.)

Eight weeks before admission there appeared symptoms referable to the same disease of the right lower extremity, an ulcer appearing at the inner side of the right heel. On March 21, 1905, the right leg was amputated for advancing gangrene of the right foot.

March 10, 1910. I found evidence of the involvement of the left upper extremity. He says that he has had trouble in his left arm and in the fingers and forearm for several months, there having been pain in the fingers, followed by swelling and redness. Then a bleb appeared at the tip of the index finger, which was incised by a physician. Shortly after this the wound became much worse and sloughing took place. About the same time a black spot

appeared over the back of the middle finger. Neither middle nor index finger has improved, and it is for these that he seeks relief.

After admission the gangrene rapidly spread, the pain becoming excruciating, and the forearm was amputated through its upper fourth.

The ablated forearm (Fig. 4) showed complete occlusion of both radial and ulnar arteries. The typical lesions of thrombo-angiitis obliterans were present.

Four years later, April, 1914, the patient was again admitted to the wards of Mt. Sinai Hospital in a condition of stupor. The notes taken read as follows: "Both legs and the left arm have been amputated. Speech is incoherent and there are evidences either of some cerebral lesion or of an arterial lesion in the brain. The condition of the right hand is of particular interest. Nowhere is there any evidence of ulcer or gangrene. The skin of the right hand is dry and atrophic. The fingers have a tapering apperance. The skin has lost its elasticity, the subcutaneous tissues have withered, and neither the radial nor the ulnar arteries are palpable. The brachial artery, too, gives but the slightest impression of the presence of pulsation."

Here, then, is a case in which two distinct clinical pictures were evolved in the course of the obliterative vascular disease, one exhibiting gangrene of an upper and two lower extremities, and the other demonstrating the unusual phenomenon of extreme atrophy of both hands and forearm.

VI. Cases Simulating Scleroderma and Sclerodactyly. Perhaps most interesting of all are those cases in which the vascular occlusion has led, by virtue of the effects of malnutrition, to a condition of dystrophy, the clinical picture being akin to that of sclerodactyly. In fact we have had occasion to observe a most pronounced example of this manifestation in a patient in whom the diagnosis of scleroderma was made by expert dermatologists.

Case X.—I. L., aged thirty-five years, was admitted to the surgical service of Mt. Sinai Hospital on October 1, 1906, with a typical history of thrombo-angiitis obliterans of the left leg. There was absence of pulsation in the dorsalis pedis and complete gangrene of the second toe, necessitating amputation. Pathological examination of the vessels of the amputated legs showed the typical lesions of thrombo-angiitis obliterans.

June 29, 1907. He was again admitted to the hospital, complaining of intense pain in the right leg which showed the symptoms of ischemia on elevation, redness in the dependent position, but no evidence of trophic disorder or gangrene. The patient begged that the limb be taken off, and the right leg was, therefore, ablated through the middle third. Pathological examination showed here, too, the typical lesions of thrombo-angiitis obliterans.

December 17, 1909. He entered the hospital complaining of trouble with his right hand and arm. For several months he has been unable to use it properly, the muscles having become stiffened. He thinks, too, that a marked diminution of the size of the hand and arm has taken place.

On physical examination the picture presented by the right arm is striking. The fingers have the typical appearance of the skin in scleroderma. Motion of the distal phalangeal joints is markedly impaired in extent. The skin is atrophic and dry and the circumference of the fingers of the right hand is distinctly diminished. Both the radial and brachial pulses are absent. The brachial artery can be felt as a hard cord, and can be traced as far as the axilla. In the axilla there is a distinct pulse.

The left hand shows no trophic disturbances, no ulcers, but the radial and ulnar pulses are absent. The brachial pulse is fairly good.

In order that we may thoroughly comprehend the points that distinguish the vasomotor and trophic disturbances dependent on organic arterial lesions from those of Raynaud's and allied diseases it may be best to pass rapidly in review the salient features of the symptomatology as they were exemplified by the above patients.

Collecting the cases in which vasomotor symptoms predominate we have, on the one hand, those in which the symptoms of thrombo-angiitis obliterans of the lower extremities are well marked and, on the other hand, those in which we are compelled to investigate very carefully in order to elicit evidences of vascular occlusion.

The symptoms simulating Raynaud's disease and acro-asphyxia are cyanosis of the finger tips, coldness of the fingers with or without trophic disturbances, and alternating cyanosis and rubor, involving the fingers or the whole hand. Rather characteristic in the symptomatology of thrombo-angiitis is the apparent dependency of the vasomotor symptoms upon variations in temperature, the chronicity of the manifestations, the absence of pain in some of the cases, and the absence of paroxysmal nature of the attacks so characteristic in Raynaud's disease.

When we turn to those patients in whom the trophic disturbances seem to be unassociated with evidence of vasoconstriction and vasodilatation we note that there is merely a history of the development of a spontaneous ulcer of the fingers. It seems more than likely that in many of these the history of the absence of the vasomotor phenomena would be found unreliable if it were possible to observe the cases throughout the whole course of the disease. Future observations will probably support my belief that here, too, some manifestations of deranged vasomotility do occur.

When we consider the largest group, namely, that in which gangrene of small or greater extent develops, we find that some cases may be mistaken for simple paronychia. Others claim that the development of a gangrenous patch or of the felon was preceded

for a long time by distressing pains in the tips of one or more fingers. The vasomotor symptoms may be absent or the cyanosis and redness may be quite striking. The following sequence of symptoms may be observed and is interesting, because pain and trophic disturbances alone are complained of. The onset is marked by severe pain in the tip of a finger. This is superceded by atrophic changes in the skin, the development of a dry, hard patch, mortification, and also formation of an ulcer. In still other cases the similarity with Raynaud's disease is even more marked, for the symptoms are pain, cyanosis, rapidly followed by gangrene.

More rarely do we meet with those interesting examples of the effects of arterial occlusion in which the development of intense atrophy of a hand or limb or the production of the typical picture of scleroderma and sclerodactyly is the significant feature of the clinical picture.

A careful clinical study of the disease, thrombo-angiitis obliterans, will dissipate all doubt as to the possibility of separating this disease, as a clinical entity, from all those neurogenic varieties of vasomotor and trophic disorders that may be clinically confounded with it. It would be too extensive to dilate upon the symptomatology of thrombo-angiitis obliterans in this paper, and, therefore, I shall confine myself to the consideration of those essential features on which the recognition of the disease depends, and which will be seen to be the effects of the obliterated condition of the arteries.

Thus characteristic for the disease are the following groups of symptoms: (1) the disappearance of the pulses, particularly the dorsalis pedis, posterior tibial and popliteal, more rarely the femoral, radial, and ulnar; (2) the development of typical manifestations of impaired circulation, to wit: blanching of the lower extremities when these are elevated above the horizontal, hyperemia (rubor) or reddening of the foot in the pendent position (a chronic condition which I have elsewhere termed erythromelia) during certain stages of the disease, and trophic disturbances, such as impaired growth of the toe nails, slightly atrophic condition of the skin, ulcers, and gangrene; (3) true vasomotor phenomena of transitory nature, such as alternating syncope, rubor, coldness, apparently independent of those chronic changes that have been cited above and that are distinctly traceable to the occluded condition of the arteries and veins; (4) the symptoms of pain, either in the form of intermittent claudication (pain in the calf of the leg or in the foot on walking with cessation when the limb is at rest) or the severe pain that is associated with the advent of trophic disturbances, especially with ulcers and patches of gangrene; (5) the slow course of the disease, symptoms of intermittent claudication or pain, preceding the development of trophic disturbances for months and years; (6) the fact that more than 99 per cent. of the cases occur in Polish, Galician, or Russian Hebrews, and that almost always young males

between the ages of twenty and thirty are taken with this disease; (7) the onset of symptoms in the lower extremities, one of the legs being first affected; (8) the comparative infrequency of involvement of the upper extremities; (9) the association of a peculiar type of migrating phlebitis in the territory of the external or internal saphenous, less frequently in the larger veins of the upper extremities characteristic in about 20 per cent. of the cases; (10) the slow but steadily progressive course, leading in a large majority of the cases to amputation of at least one limb, not infrequently of both lower extremities, and in rarer instances to amputation of one of the upper extremities as well.

Even a rapid review of the salient symptoms of this interesting malady would seem to suffice to leave the impression that it could hardly be mistaken for other diseases. And were it not for the fact that certain symptoms, closely resembling typical vasomotor phenomena, may persist for weeks and years in this disease, confusion with the true neurogenic vasomotor process would scarcely ever arise. The chronic condition of redness in thrombo-angiitis obliterans can be explained as due to dilatation of the superficial capillaries, this being a compensatory phenomenon making for an adjustment of the impaired circulation. This chronic redness or rubor may be mistaken for erythromelalgia or for the rubor of Raynaud's disease. The fact that it is associated with other evidences of closed vessels and the other characteristic features above mentioned, together with the circumstance that the redness disappears at once upon elevating the extremity, will make the recognition of its nature possible.

In addition to this more or less chronic or permanent sign of deranged vasoconstriction, other phenomena which are truly vasomotor in nature may frequently be associated in thrombo-angiitis, and it is these that must be differentiated from similar phenomena accompanying Raynaud's disease, erythromelalgia, scleroderma, sclerodactyly, and acrocyanosis.

If we do not overestimate the importance of single manifestations of vasomotor irritation, but regard as more significant the clinical course and the symptoms in their totality, we will not fail to separate very clearly in our minds the true vasomotor neuroses from the organic vascular disease attended with vasomotor phenomena.

In order that a differential diagnosis may be clearly presented, let us briefly recapitulate the typical course of a case of Raynaud's disease. Raynaud's disease is an affection whose pathology has not as yet been definitely determined, the lesion doubtlessly residing somewhere in the central nervous system. Its clinical characteristics may thus be summed up:[1] Somewhere in the peripheral portions of the body (so-called acra) there occurs more or less

[1] Cassirer, Die Vasomotorisch-tropischen Neurosen (S. Karger, Berlin, 1912).

severe pain not confined to distinct nerve territory, usually affecting symmetrical parts, attacks of vasomotor disturbance being part of the syndrome. These latter are (1) syncope, asphyxia, or local rubor, and (2) severe trophic disturbances, usually in the form of gangrene of the parts first affected with symptoms. The course is an intermittent one, for there may be completely free intervals; but in some instances, evidences of disturbed vasomotility may persist. The disease may consume itself in one attack or several attacks may occur in succession. Objectively, sensory disturbances are usually absent, as well as paralysis, although other evidences of disturbed vasomotor innervation, such as aphasia, hemoglobinuria, arthropathy, may occur. Usually neuropathic individuals are affected. The organic vascular changes, as well as the lesions of the nervous system, reported occurring in some of the cases, have, doubtless, no causative relation with the disease.

It is true that there are still some who cling tenaciously to the theory that some lesions of the peripheral arteries may account for the symptoms of Raynaud's disease. In support of this view certain anatomical findings have been cited as strong arguments by those who believe that a definite anatomical lesion in the peripheral vessels is irresistible testimony against pure hypothesis. A careful analysis of the cases in question, as made by Cassirer, shows that reported organic alterations in the vessels will not suffice to explain the symptoms any more satisfactorily than the theory of a central nerve affection of the sympathetic system. Whereas in thrombo-angiitis obliterans the territory manifesting symptoms corresponds to that containing the diseased vessels, we find that no such relation exists where vascular lesions are associated with Raynaud's disease.

For the clinical diagnosis of thrombo-angiitis we must depend upon (1) the racial (Hebrew) and sex (male) predilection; (2) the early involvement of the lower extremities; (3) the early symptoms of pain or intermittent claudication; (4) the presence of migrating phlebitis; (5) the evidences of pulseless vessels; (6) the presence of blanching of the extremity in the elevated position; (7) the existence of rubor in the dependent position; (8) the relation of the hyperemic phenomena to posture; (9) the absence of simultaneous, symmetrical involvement; and (10) the slow, progressive chronic course terminating in gangrene.

In Raynaud's disease we will note the following features: A sudden onset of the first stage of local syncope or regionary ischemia involving usually the fingers, more rarely the toes, and occasionally the margins of the ears or the tip of the nose with coldness and blanching; associated sensory phenomena, paresthesia, and pain; a comparatively short duration of the vasomotor and sensory manifestations, their intermittent character with return to normal between the attacks; the symptoms of local asphyxia attended with

local depression of temperature and swelling of the parts involved; the disappearance of the asphyxia with substitution of reactive hyperemia and a third stage of dry gangrene. Characteristic for this disease as well as for the cases of scleroderma and sclerodactyly is the striking atrophy of the ends of the distal phalanges.[2] The changes in the bones can be well demonstrated by Roentgen-ray examination, atrophy and disappearance of large portions of the end-phalanges being distinctive and diagnostic features. In our own experience the alterations in the bones could be detected early in the disease, probably developing simultaneously with the other trophic disturbances.

If we analyze the symptomatology of the cases of thrombo-angiitis cited above we will find, that the differential diagnosis of this condition from the vasomotor neuroses is only difficult in those cases where we cannot rule out the possibility of the association of the two diseases. It will be noted that where coldness and cyanosis are complained of, a distinct dependency on temperature or other environmental condition can often be elicited or that pain is absent. The presence of vessels changes and the history of the involvement of a lower extremity at once clear up the diagnosis.

Where trophic changes alone are present, the absence of symptoms referable to the central nervous system speaks decidedly against nerve lesions. The relation of the vasomotor symptoms to the position of the limb will in other cases be of value in explaining the nature of the symptoms.

How can we explain the occurrence of true vasomotor phenomena such as do not seem to owe their existence to the mechanical effects of impaired circulation? The blanched appearance that is a sequence of an obstructive condition of the arteries, and which can be demonstrated by elevation of the leg, and in bad cases can even be elicited in the horizontal position, is a phenomenon easily explicable on the theory that the avenues of arterial supply are cut off through extensive obturation of the arteries. Many clinical and experimental observations have been gathered that speak in favor of this view. So also is the rubor not a true vasomotor phenomenon, but a sign of chronic vasodilatation of the superficial capillaries and is compensatory in nature.

On the other hand, veritable symptoms of disturbed vasomotility can be associated with thrombo-angiitis obliterans. That these should occur is not surprising when we call to mind that not only have intense and extensive destructive, pathological alterations taken place in the most important arteries of a limb, but that the accompanying nerves are frequently bound down by a dense mass of cicatricial tissue and have undergone severe fibrotic changes. Although the mechanism of the irritative and exhaustive vaso-

[2] Compare with changes in sclerodactyly (Figs. 5 and 6).

motor phenomena is not clear, the total disorganization of the vascular innervation in many of the cases would seem to afford sufficient basis for the possibility of the occurrence of the disturbances which we call "vasomotor" in nature.

FIG. 5.—Roentgen-ray photograph of a case of sclerodactyly, showing disappearance of the terminal phalanges.

Where signs of thrombo-angiitis of the lower extremities are unquestionably present, and where evidences of vascular occlusion in the upper extremities are lacking, although these are the site of disturbed vasomotor innervation, we may for a long time be

unable to rule out the possibility of the simultaneous occurrence of two different diseases.

The differentiation of true scleroderma from thrombo-angiitis will be rarely difficult to make. In scleroderma and sclerodactyly the first stage with hard edema is characteristic and never simulated by

FIG. 6.—Roentgen-ray photograph of a case of sclerodactyly, showing disappearance of the terminal phalanges.

cases of organic vascular disease. The second indurative stage may, however, be almost exactly reproduced by other affections. The form of scleroderma known as "sclerodactyly," because of attendant alterations in the deeper tissues, may be not unlike

thrombo-angiitis. Roentgen-ray examination of the hand in sclerodactyly offers the most valuable means of differentiating the two diseases (Fig. 5 and 6). The phalanges will very early show atrophic changes and disappearance of the terminal portions in scleroderma, sclerodactyly, and Raynaud's disease, while the bones, although somewhat rarefied, will be seen to conserve their outlines throughout the course of the disease, thrombo-angiitis obliterans, until they are disturbed by the effects of gangrene.

So far as our experience permits us to judge, symptoms of scleroderma occur only late in thrombo-angiitis when other signs of vascular occlusion have already become well developed. The recognition of the condition will then depend upon the absence of pulsation in the larger peripheral vessels, the presence of gangrene (or the history of such a condition) and of the other typical signs of obliterated arteries and veins.

In the light of our recent studies on the pathology of thrombo-angiitis obliterans we are able to state that certain characteristic morphological changes in the arteries and veins are specific[3] for this process. These occur in the deep arteries and veins as well as in the superficial veins, when these are the seat of the so-called "migrating phlebitis." Whenever migrating phlebitis is present, therefore, the excision of a portion of vein under local anesthesia followed by microscopic examination will lead to a diagnosis.

It is most probable that in Raynaud's disease and the related affections the seat of the pathological process is to be sought in the vegetative system, that is, somewhere in the vasomotor apparatus. Nor are we likely to be rewarded in a search for any organic change. The frequent return to a normal condition, observed clinically, also speaks against the likelihood of morphological or chemical alterations in the nervous system.

Whereas in thrombo-angiitis obliterans a definite and specific morphological change in the arteries and veins is responsible for the varied phenomena in the superficial capillaries, in Raynaud's and allied diseases the vasomotor and trophic disturbances are the outcome of irritative and exhaustive processes of the sympathetic nervous system.

[3] Surg., Gyn., and Obs., 1914.

THE IMPORTANCE OF THE PARANASAL SINUSES IN THE EXPLANATION OF PAIN IN THE FACE, HEAD, NECK AND SHOULDERS.[1]

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Two years ago I reported some observations on the relation of the branches and the ganglia of the fifth cranial nerve to the accessory sinuses of the nose. The material on which that study was made consisted of approximately seventy decalcified heads and parts of heads observed with Dr. Greenfield Sluder.

The work of Ladislaus Onodi,[2] came to our notice about two months later (July 18, 1912) than my report, in which he confirmed these observations, employing a different method.

In the past few years numerous studies of the accessory sinuses have been made, chiefly by rhinologists. These studies, notably those of St. Clair Thompson,[3] deal chiefly with direct extensions of suppuration through dehiscenses in the post-ethmoidal-sphenoidal walls or transference through venous or lymphatic channels of infection to the cavernous or other blood sinuses, or to the meninges.

Our efforts have been to show that the nerve trunks and ganglia are directly or indirectly affected by the air sinus infections and that widespread referred pain springs from this district, pain which is treated without result unless its origin be recognized.

The anatomical relationships described in the above-cited text, I believe explain the mode of production of these pains.

Recently, Dr. C. A. Gundelach, of St. Louis, has devised a method of directly inspecting the interior of the sphenoidal sinuses much in the same way that a bladder is viewed through a cystoscope. This has enabled us to see during life not only the condition of the lining membrane but the position of the Vidian in the floor and the convex elevation marking the position of the second division of the fifth on the outer wall of the sinus.

Our clinical observations, carried on at the same time as the anatomical study, have been very numerous and have served to confirm our belief that the thickness of the sinus walls and the close or remote relationship of the trunks and ganglia to diseased sinuses has a constant significance.

The widespread distribution of the referred pain cannot be explained on anatomical grounds, according to our present knowledge. This phenomenon is still somewhat a mystery in other

[1] Read before the American Neurological Association, May 8, 1914.
[2] Archiv. f. Laryngologie (zweite heft).
[3] Trans. Med. Soc., London, 1906, vol. xxix.

parts of the body also, although much light has been shed upon this subject in recent years by the studies of Dr. Henry Head and others.

In 1908 Sluder published[4] a description of sphenopalatine ganglion neuralgia which runs as follows:

"Inflammation in the nasal structures (accessory sinuses, sometimes nasal membrane) produces by its extension to, or transmission of its toxins, the ganglion, a symptom-complex, partly neuralgic (painful), and partly motor, sensory, and gustatory. The neuralgic picture is pain in the root of the nose and in and about the eye, in the upper jaw and teeth (sometimes lower jaw and teeth), extending backward under the zygoma to the ear, frequently making earache and pain in the mastoid; extending thence to the occiput, neck, shoulder-blade, breast, and when severe to the arm, forearm, hand, and fingers, with sometimes a sense of sore throat on that side. Rarer additions to this picture are itching of the skin of the upper extremity, taste disturbance (parageusia), a sense of stiffness and muscle weakness in the upper extremity, and fortification scotomata."

Mild cases are described as a sense of tension in the face and stiffness or "rheumatism" in the shoulders. It may appear as constant pain with exacerbations or it may stop and reappear cyclically as a migraine; or it may stop and reappear with the stabbing sharpness of a "tic."

The motor phenomena are changes in the appearance of the soft palate. Its arch is higher on the affected side, and the dimple which forms in the rhaphe just above the uvula in the act of gagging is deflected to the well side. The uvula is inclined to the well side.

The sensory phenomena are slight blunting of the tactile sense of the soft palate, pharynx and tonsils, with like condition of the membrane of the nose of the affected side.

The gustatory phenomena are confined usually to a slight blunting of the sense of taste on that side. Parageusia is rare.

Heretofore we have felt that the complete picture was so rare as to be never presented by one case. I have recently found, however, examples of the entire symptom complex. I have also observed a large number of modifications of the complex, depending, I think, upon the anatomical variations present.

The following case, which has been followed since 1905, will serve as a type of the complete picture.

Miss S., aged twenty-seven years, had for several years suffered "off and on" with pain beginning at the root of the nose, involving the upper jaw and teeth (occasionally the lower jaw and teeth), extending backward to the tip of the mastoid, and most intense about

[4] New York Med. Jour., May 23, 1908, pp. 989–990.

5 cm. posterior to this point. When she first came under observation, in 1906, the nose was negative in every particular. Some months later a post-ethmoidal-sphenoidal inflammation developed on the left side. Almost simultaneously the old pain, which had almost disappeared, returned. It involved the root of the nose, the cheek, the mastoid tip and a little behind it, the neck, shoulder-blade, shoulder, and arm—all in greatest severity.

Soaking a strong solution of cocain into the tissues overlying the sphenopalatine ganglion always stopped the pain, and the relief would often last for several days.

The pain was on the left side. The arch of the soft palate was markedly higher on the left; the uvula was deflected to the right. The soft palate and the pharynx down to the level of the lower part of the tonsil were somewhat less sensitive on the left side to contact with a lock of loose cotton. On the floor of the left nostril anteriorly cotton was not so well perceived. In the middle and anterior third of the tongue the sense of taste for sugar, sodium chloride, citric acid, and quinin bisulphate was less acute on the left than on the right.

Many exacerbations and remissions occurred. Many injections of plain alcohol were attempted. The total result has been a cure. The case illustrates not only the characteristic features, but the sometimes extremely discouraging failures one must meet before getting a complete result. For three years she has been well.

We meet with certain cases which are characterized by a sense of tension and soreness in the neck, from the occiput to about the seventh cervical vertebra, radiating into one or the other shoulder, in which there is very slight pain in the face or about the ear. Movement of the head forward or from side to side is painful and there is a sense of lameness and muscle soreness in the shoulder and arm. Both golf arm and violinists' cramp have been diagnosed in such instances.

There is often a sense of depression and irritability amounting to demoralization. I have had men and women of the highest type tell me that although the pain was not intense that the nagging quality of it made it impossible for them to keep control of their emotions. The sensory distress is variously described as clawing, grabbing, pulling, or as tension which never lets loose and fatigue which does not disappear with rest.

Headache, which usually accompanies the neck and shoulder pain, is inconstant. No sensory or motor changes need accompany the picture. The following will serve to illustrate this type:

J. A., aged twenty-six years, a healthy, single man, had suffered, on May 16, 1912, five years with severe discomfort in the left side of the back of his neck. His collar annoyed him constantly on that side. Some months after the pain began it extended into the left shoulder and later to the left arm and hand. Before I

saw him he had sometimes had pain about the eyes, which led him to consult an oculist, but without relief. His left ear sometimes felt "filled up." He never had any discharge from his nose. Cocainization of the area of the sphenopalatine foramen relieved the pain for a time. Injection of the sphenopalatine ganglion with approximately ten drops of a 5 per cent. carbolic in 95 per cent. alcohol was followed by some discomfort at the time, which lasted from seven to ten days. Then followed marked betterment clinically.

The relief, however, was not complete. Reinjection three months later was followed by further betterment. A third injection at about the same interval was followed by a practical cure. A coryza six months later reëstablished his discomforts but in a lesser degree. A fourth injection was given which seems thus far to have completed the cure. For the past year he has been free from pain except a slight degree, which has been provoked from time to time by coryzas of greater or lesser severity.

We could demonstrate no motor or sensory changes in this case which we interpret to have been unquestionably explainable by an exposure of the Vidian nerve itself in the sphenopalatine foramen. This is not an infrequent exposure, as may be very readily determined by an examination of a series of skulls. The Vidian in this class of skulls must proceed farther forward and slightly outward before it reaches the ganglion. It is accessible from the sphenopalatine foramen for cocainization or treatment, and may readily be injected from the foramen itself or from under the tip of the middle turbinate. We have proved this fact by the injection in cadavers, the specimens being injected as in the veritable operation, and subsequently decalcified and sectioned.

We believe this to be a case of Vidian neuralgia. Admitting this, it becomes self-evident that exposure of the Vidian in the floor of the sphenoidal sinus, either by dehiscense of the upper arc of the Vidian canal, or through a thin plate of bone, will produce this same picture, the point of irritation being posterior in this instance to that in the first instance. In the first instance cocainization of the area of the sphenopalatine foramen will stop the pain, but in the second instance will be without effect. In the second instance intrasphenoidal applications of analgesic remedies will be effective.

A type of similar kind is illustrated in the case of Mrs. F., aged forty-seven years. She came under my observation October 8, 1913. For two weeks she had suffered from a painful neck, from the occiput to the seventh cervical vertebra. Movement either active or passive increased the pain. There was tenderness to pressure over the cervical spines and extending over the muscles of the left side of the neck. Later the pain extended to the left shoulder and was so constant and harassing as to demoralize the

patient. Psychically the depression seemed out of proportion to the pain described. This had been a usual observation in this type.

Combinations of internal and local remedies, salicylates, iodides, moist heat, massage, electricity, etc., were thoroughly tried, without effect.

Cocainization of the area of the sphenopalatine foramen, particularly its posterior half, exposure of the Vidian district, very much reduced the pain in ten minutes.

Later examination disclosed a suppurating sphenoidal sinus. Treatment addressed to the sphenoid and to the exposure of the district of the Vidian has resulted in nearly complete relief for the greater part of the time.

The relief has been even more striking psychically than physically, and a sense of well-being and zest in life customary to the patient have returned.

Optic disk swelling associated with headache, vertigo, and nausea is such an important symptom-complex indicative of intracranial tension, and the presence of post-ethmoidal-sphenoidal infection often so obscure, that we may possibly accept a reminder of what may happen, and in doubtful cases direct our attention to the exclusion of this field before we advise a decompression.

The following will illustrate such a case:

S. P. C., a vigorous lad, aged sixteen years, came to me from Dr. Post, ophthalmologist, with a history of pain in the eyes and befogged vision for five weeks. A gradually increasing headache, with vertigo, accompanied the failing vision. There had been no vomiting. Vision was 1/92 in either eye. There was swelling of the disks, four diopters in the right and five in the left. General neurological examination negative.

Rhinological examination at first reported negative, subsequently disclosed post-ethmoidal-sphenoidal suppuration. Post-ethmoidal operation was performed by Dr. Loeb.

There was prompt subsidence of the optic swelling and rise in visual clearness, with disappearance of headache. Vision in five days had risen to 20/24° and the swelling had receded to one diopter in either eye in the same period. This case was seen in August, 1912. The boy recovered and remained perfectly well during the next several months. Not content with the conditions of life in his home he departed for the Pacific Coast and has been lost sight of.

It is well to say that these are not simple and easy cases to manage. They require painstaking investigation for correct diagnosis. Treatment is at first often disappointing. A certain dogged persistency, not always easy to maintain, is required to meet the failures and baffling eccentricities of reaction. Curious reversals of reaction occur, some of which I am laboring with now, and which will be dealt with in a subsequent paper.

My object in this report has been to present three clear types, with which I have had a large experience, and which I have learned to manage with a degree of success that is satisfactory.

They are infinitely more difficult to deal with than tics or neuralgias of the second and third division, which may be cured by injection from the zygoma. The nerve fibers are readily destructible by alcohol, but the nerve cells are very resistent. These points were proved by Dr. Otto May[5] in experiments on cats, dogs, and goats.

Another feature which should be remembered is that the sphenopalatine ganglion is small (5 mm.) and by no means easily struck, whether approached with a straight needle from below the posterior tip of the middle turbinate or by means of a curved needle entering through the sphenopalatine foramen, and whether these attempts be made under the view of the Holmes pharyngoscope, because it is impossible to know the exact position of the ganglion in any individual.

Dr. Sluder and I have proved in a series of experiments on the cadaver that the ganglion or its immediate environment may, however, be struck as an average procedure. Our injections were made with carmine and Prussian blue, the specimens then decalcified and sectioned macroscopically.

It is probable that instillation of alcohol into its immediate environment is efficacious, but not to the same degree that follows when it is placed directly in its substance.

For these reasons I have long since ceased to be discouraged by an incomplete or unsatisfactory result from a first injection.

Some years ago I felt that the result of an injection was complete in ten days. I have since changed my ideas on this subject, and now believe that it requires three months before conclusions can be reached.

These are my feelings since carbolic acid has been added to the alcohol for its analgesic effect. It seems that the effect of carbolic acid is not complete short of three months. At the end of this time I have the case reinjected if the result has not been satisfactory.

It is, of course, self-evident that the shoulder-arm-hand syndrome may be produced by a mediastinal pressure, which must be borne in mind.

[5] British Med. Jour., August 31, 1912.

FUNCTIONAL TESTS IN EXPERIMENTAL TARTRATE NEPHRITIS.[1]

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and

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Pathology of Tartrate Nephritis. Underhill, Wells, and Goldschmidt[2] succeeded in producing a severe form of acute nephritis in rabbits by subcutaneous injections of racemic tartaric acid. According to these observers, vacuolization of the epithelium of the convoluted tubules is the essential lesion in the earliest stages. Necrosis rapidly follows the vacuolization, so that nearly all the convoluted tubules may soon become necrotic. The glomeruli are practically uninjured. It was suggested by these investigators that tartrate nephritis offers a specially favorable opportunity for physiological studies, inasmuch as the convoluted tubules are practically all destroyed and the glomeruli left intact.

Pearce and Ringer,[3] from a study of tartrate nephritis in dogs, state that the most striking change is necrosis of the convoluted tubules, with fat in the loops of Henle and sometimes in the collecting tubules. They found exudative glomerular lesions in about one-half of the animals in which the tubular lesions were severe. Tartrate nephritis was purely tubular in only about one-half of their cases.

In our series of forty-five cases of experimental tartrate nephritis in rabbits the tubular lesions in the severe cases are essentially the same as those described by Underhill, Wells, and Goldschmidt. A few hours after injection of the tartrate the epithelium of the convoluted tubules may show extreme vacuolization. This condition was pronounced in one animal killed five and a half hours after the injection and in another killed two and a half hours after the injection. (See Figs. 1 and 2). The exact time of the first appearance of vacuolization was not determined. Necrosis and fatty metamorphosis begin the first day and advance rapidly. If the animal lives three or four days, fat may be a prominent feature. It is specially conspicuous in the convoluted tubules, but may be found in any tubule. Rarely there are some fat droplets in the glomeruli.

[1] Aided by a grant from the Research Fund of the University of Minnesota.

[2] Tartrate nephritis, with special reference to some of the conditions under which it may be produced, Jour. Exper. Med., 1913, xviii, 322.

[3] A study of experimental nephritis caused by the salts of tartaric acid, Jour. Med. Research, 1913, xxix, 57.

When necrosis is well established there is usually no suggestion of the original vacuolated condition.

We have found a little hydropic degeneration (vacuolization) after the first day, but it seems to be a prominent lesion only during the first half day.

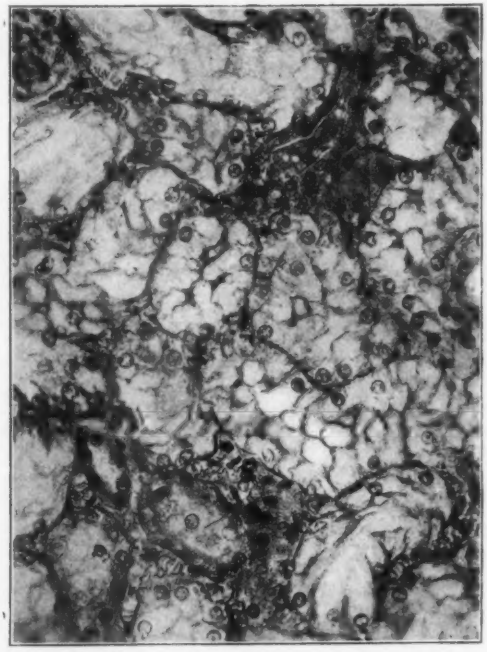

FIG. 1.—Kidney of rabbit five and a half hours after tartrate injection. Zenker, paraffin, hematoxylin, and eosin. Hydropic degeneration is very pronounced. The small tubules of the collecting type show little involvement. Photomicrograph.

The left kidney of a rabbit was removed seven and a half hours after the tartrate injection. This kidney showed extreme hydropic degeneration. Forty-eight hours after the nephrectomy the rabbit was killed. The right kidney showed necrosis of nearly all the convoluted tubules. No sign of hydropic degeneration was to be seen. It is therefore clear that the first lesion in tartrate nephritis is a hydropic degeneration, and that this condition gives place to fatty metamorphosis and necrosis in the later stages.

Hydropic degeneration involves all the convoluted tubules in all parts of the cortex. The first tubules to undergo necrosis are those near the capsule. The tubules in the deep part of the cortex next to the medulla become necrotic only in severe cases, though

they may show marked degenerative changes. When all the convoluted tubules are necrotic there is usually an anuria so that no functional tests can be made. As a rule our functional tests were made on kidneys in which over half the convoluted tubules showed necrosis and the remainder fatty and granular degeneration.

FIG. 2.—Small area from Fig. 1 under high magnification. Photomicrograph.

Some of the cases show swollen, opaque, cloudy kidneys. These have the gross features of cloudy swelling. When crushed specimens of fresh tissue are examined under high magnification it is seen that nearly all the tubules are granular. This granular condition is present in kidneys that are dark and reddish as well as in those that are pale and cloudy. The granules are least conspicuous when necrosis is most extensive. Of course, many of the granules are fat droplets. These may be identified by their insolubility in potassium hydroxide. But the albuminous granules are always present and frequently dominate the picture. These fade in potassium hydroxide but do not completely disappear. They are unlike the granules seen in the normal kidney. This granular condition of the epithelium is constantly present in tartrate nephritis of the mild

as well as the severe types. It is best seen in crushed specimens of fresh tissue. It may be called a granular degeneration. The swollen, cloudy kidneys that show this microscopic appearance would usually be regarded as examples of cloudy swelling.

As regards the glomerular lesions, there were seven animals in our series of forty-five in which precipitated serum could be seen in some of the capsular spaces in every section. To what extent this indicates functional disturbance in the capsular epithelium we cannot determine. The glomerular tufts are often congested and rarely fat droplets can be demonstrated in them; but they are never found necrotic. And even in the most extreme cases of glomerular involvement there are always many in every section that are anatomically intact. It is probable that there is moderate glomerular injury in some cases of tartrate nephritis; but one may exclude these cases and use only those in which there are no anatomical glomerular lesions.

Schlayer and Takayasu[4] believe that the glomeruli may be functionally deranged even though they show no histological lesion. They therefore discard the histological evidence and estimate the glomerular function by testing the amount of contraction and dilatation of the renal vessels and the diuresis in response to stimulation. But as v. Monakow[5] has in part suggested, it is doubtful whether Schlayer's test is any better than the histological appearance. The capsular epithelium of the Malpighian corpuscle might be able to perform its functions even though the bloodvessels of the kidney do not respond to stimulation.

MATERIAL AND METHODS. Experimental tartrate nephritis has been studied in forty-five rabbits. In the latter half of our work we have used only racemic tartaric acid. In our first experiments Merck's dextrotartaric acid was used. Merck's preparation will produce a severe nephritis, but it is much less certain in its action than the racemic acid. It is also easier to produce a complete suppression of phenolsulphonephthalein excretion with the racemic acid. We have usually employed 0.4 gm. to 0.7 gm. of racemic tartaric acid neutralized with sodium carbonate and injected subcutaneously according to the method described by Underhill, Wells, and Goldschmidt. 0.3 gm. of the acid often produces complete suppression of the phthalein excretion, but much larger doses occasionally fail. In general a large dose is much more apt to produce a severe nephritis than a small dose. The animals were fed in the usual way during the experiments.

Some rabbits develop considerable resistance to tartrates. If they recover from the first dose much heavier doses are required

[4] Untersuchungen über die Funktion kranker Nieren, Deutsch. Arch. f. klin. Med. 1909, xcviii, 17.

[5] Beitrag zur Funktionsprüfung der Niere, Deutsch. Arch. f. klin. Med., 1911, cii, 248.

subsequently to produce a nephritis. In one rabbit an initial dose of 0.6 gm. reduced the phthalein excretion to 6 per cent. for the first two hours. After the phthalein excretion had returned to normal, repeated doses of tartrate were given, some as high as 1.5 gm., but no signs of nephritis appeared.

Only those animals have been used for further functional tests in which the nephritis produced was of such a degree as to cause complete or almost complete suppression of phthalein excretion. This condition is usually present as early as three hours or less after the injection of the tartrate, and continues until the death of the animal. An injection of phthalein was given every forty-eight hours during the experiment. Two rabbits that at one time showed complete suppression of phthalein, recovered completely.

PHENOLSULPHONEPHTHALEIN. Rowntree, Fitz, and Geraghty[6] have shown that this dye is excreted by the tubular epithelium in the frog's kidney. They have also shown that the elimination of phthalein is greatly reduced in experimental passive congestion whenever the congestion is made severe enough to produce marked tubular injury. In moderate passive congestion there is no marked change in phthalein excretion.

Rowntree and Geraghty[7] and Rowntree and Fitz[8] have given abundant clinical evidence that the excretion of phthalein is decreased in almost all forms of nephritis, and in general that the amount excreted corresponds to the degree of functional involvement of the kidney. Inasmuch as human nephritis never shows complete destruction either of all the tubules or of all the glomeruli it is difficult to decide from this material by what route the phthalein is eliminated.

Eisenbrey[9] found marked reduction of the phthalein excretion in experimental nephritis in dogs, produced by uranium nitrate and potassium chromate.

Austin and Eisenbrey[10] state that in experimental nephritis in dogs the anatomical picture bears no definite relation to the amount of phthalein excreted. These observers had no cases of zero phthalein elimination.

In our experiments twenty-three rabbits showed either no excretion of phthalein or a faint trace for the first two hours. All of these animals had very severe nephritis. In over half of these the

[6] The effects of experimental chronic passive congestion on renal function, Arch. Inter. Med., 1913, xi, 121.

[7] An experimental study of the functional activity of the Kidneys by means of Phenolsulphonephthalein, Jour. Pharmacol. and Exper. Therap., 1909–10, i, 579.

[8] Studies of renal function in renal, cardiorenal, and cardiac diseases, Arch. Inter. Med., 1913, xi, 258.

[9] A study of the elimination of phenolsulphonephthalein in various experimental lesions of the kidney, Jour. Exper. Med., 1911, xiv, 462.

[10] Experimental acute nephritis: The elimination of nitrogen and chloride compared with that of phenolsulphonephthalein, Jour. Exper. Med., 1911, xiv, 366.

animals were not allowed to die of nephritis but were killed immediately after a phthalein test, so that the corresponding anatomical picture could be studied. The lesions in the convoluted tubules are either severe hydropic degeneration, fatty metamorphosis, necrosis, or a mixture of fatty metamorphosis and necrosis. Granular degeneration is associated with all the changes just mentioned. The glomerular changes were discussed above. In tartrate nephritis

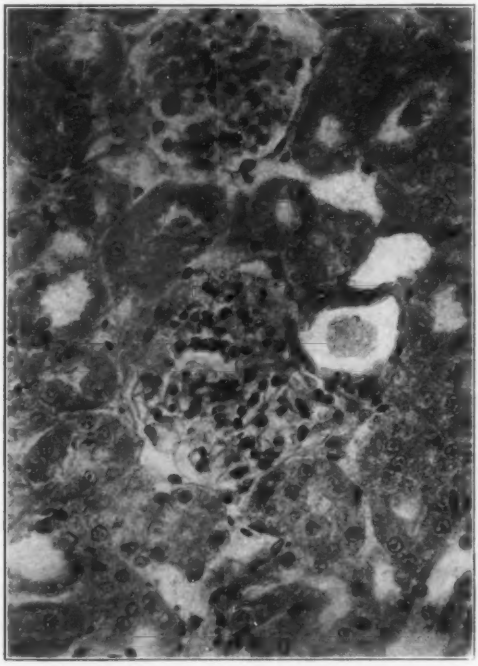

FIG. 3.—Kidney of a rabbit injected with tartrates the preceding day. Zenker, paraffin, hematoxylin, and eosin. The animal was killed immediately after a test which showed a 5.8 per cent. phthalein excretion for two hours. The epithelium is very granular, but there is no necrosis. Photomicrograph.

a trace or a zero elimination of phthalein corresponds always to a very severe injury of the renal tissue. There may, however, be little or no necrosis.

One of our animals was killed immediately after a test which showed 5.8 per cent. phthalein for the first two hours. All the epithelium was decidedly granular, but there was not much necrosis, vacuolization, or fat. (See Fig. 3.) Another animal, killed immediately after a test showing 6 per cent. elimination of the dye for two

hours, had a rather marked hydropic degeneration. These two experiments indicate that different histological pictures may be associated with the same degree of functional derangement. Apparently the excessive accumulation of granules in the cytoplasm interferes with cell function even as vacuoles do.

Large quantities of urine, containing various normal constituents, may be excreted when the phthalein excretion is zero. In many of

FIG. 4.—Kidney of a rabbit forty-eight hours after tartrate injection. Zenker, paraffin, hematoxylin, and eosin. The convoluted tubules are almost entirely necrotic. The intermediate tubules are granular, but otherwise appear normal. This is the type of kidney we have used to a considerable extent in our functional tests. Photomicrograph.

these cases the lesions are almost entirely tubular. It is, therefore, highly probable that phthalein is eliminated by the tubular epithelium.

A zero phthalein excretion does not necessarily mean a fatal prognosis in tartrate nephritis. Two rabbits showing this condition at one time have recovered completely so far as can be determined by phthalein excretion and general health. Rowntree[11] reports

[11] The study of renal function: The prognostic value of studies of renal function, AMER. JOUR. MED. SCI., 1914, cxlvii, 352.

that he has seen 2 cases of chromate nephritis in rabbits showing zero phthalein excretion recover in a short time.

INDIGO-CARMINE. Rowntree, Fitz, and Geraghty[12] state that there is no additional information to be had from the use of indigo-carmine when phthalein is used, since it is excreted in amounts roughly corresponding to the amount of phthalein and is much more difficult to estimate colorimetrically. Rowntree and Geraghty[13] give a discussion of this test.

Our results also show parallelism between the excretion of phthalein and indigo-carmine. Two rabbits which showed a faint trace of phthalein for one hour were given indigo-carmine immediately. Only a trace of the dye was eliminated in each case. Three other rabbits which showed complete suppression of phthalein for the first hour likewise showed complete suppression of indigo-carmine injected immediately after the phthalein test. Phthalein and indigo-carmine are apparently excreted by the same structures in the kidney.

METHYLENE BLUE. A discussion of this test is given by Rowntree and Geraghty[14] (p. 585). The excretion of this dye is said in general to run parallel to indigo-carmine. In some forms of chronic parenchymatous nephritis its excretion is said to be normal or exaggerated.

In our experiments one rabbit which showed a trace of phthalein for the first hour showed complete suppression of methylene blue. Two rabbits showing suppression of phthalein gave a trace of methylene blue. In two other rabbits both phthalein and methylene blue were completely suppressed. These results agree closely enough to prove that methylene blue is excreted in the same way as phthalein and indigo-carmine.

LACTOSE. De Bonis[15] injected a 1 per cent. solution of sodium fluoride into the ureter near the renal pelvis (Bottazzi's method). This procedure is said to destroy the medulla and all of the cortex except the glomeruli. More urine usually passes through the injured kidney than through the normal one. De Bonis[16] determined in this way that lactose may be excreted by the glomeruli. Rowntree, Fitz, and Geraghty[17] found that in the frog lactose may be excreted by the tubular epithelium. This experiment was performed by ligaturing the arterial supply of the glomeruli and then testing the renal function. (This method was first used by Nussbaum[18] in a study of renal function.) These authors also found that in experimental chronic passive congestion in dogs, lactose excretion is delayed one to two hours after intravenous injection. Marked

[12] Loc. cit. [13] Loc. cit. [14] Loc. cit.

[15] Giorn. intern, d. Science med., 1907, xxix, 446. (Cited from Rowntree and Fitz.)

[16] Experimentelle Untersuchungen über die Nierenfunktionen, Arch. f. Anat. u. Physiol., physiol. Abth., 1906, 271.

[17] Loc. cit. p. 126.

[18] Arch. f. d. ges Physiol., 1876, xvi, 179; xvii, 580.

delay in the excretion of lactose may occur when the phthalein output is normal.

Schlayer and Takayasu[19] used lactose as a vascular test in their experiments on rabbits. The normal kidney eliminates 1 gm. of lactose when injected intravenously in five and a half to seven and a half hours, average time six hours. In chromium, sublimate, and aloin nephritis lactose excretion is good in the earlier stages while the bloodvessels of the kidney react; but in the later stages when the bloodvessels no longer react its excretion time is prolonged to eight hours. No experiments showed suppression of lactose excretion.

Cases of human nephritis with delayed lactose excretion are regarded by Schlayer and Takayasu[20] as a vascular type. These authors believe that lactose and water are excreted by the glomeruli.

Rowntree and Fitz find lactose excretion delayed in all their human cases of nephritis or chronic passive congestion. In several cases they found a complete suppression of lactose excretion. These were all cases of severe nephritis. Lactose excretion in nephritis does not correspond to that of phthalein. The manner of its excretion is not yet determined.

To test the excretion of lactose we injected 3 gm. subcutaneously. The time required for the disappearance of sugar from the urine of normal rabbits after this injection varied from 13.5 to 23.5 hours in the five animals tested. The average time was twenty hours. Benedict's test for sugar was used. This is much longer than the time required to excrete 1 gm. when given intravenously. This period was found by Schlayer to average six hours in the normal rabbit.

Five animals in which the phthalein elimination was zero were injected subcutaneously with 3 gm. of lactose. The lactose disappeared from the urine in thirty-two, forty-two, forty-three, forty-eight, and forty-eight hours respectively—average 42.6 hours. This, it will be noted, is about twice the normal elimination time.

Several clinical cases reported by Rowntree and Fitz showed lactose excretion prolonged beyond twelve hours (2 gm. of lactose were injected intravenously in their cases). This period is also about twice the normal elimination time.

No case of lactose suppression has been encountered experimentally. Even when practically all the convoluted tubules are necrotic it is still excreted. Inasmuch as the destruction of the tubular part of the renal excretory apparatus is so complete in many cases of tartrate nephritis this condition affords specially clear proof that the glomeruli may excrete lactose. There is, however, no

[19] Untersuchungen über die Funktion kranker Nieren, Deutsch. Arch. f. klin. Med., 1909, xcviii, 17.

[20] Untersuchungen über die Funktion kranker Nieren beim Menschen, Deutsch. Arch. f. klin. Med., 1910–11, ci, 333.

evidence in these experiments that the tubular epithelium cannot perform this function. The delayed excretion may mean that more must now be excreted by the glomeruli since the tubules are destroyed. There is no experimental evidence to explain the complete suppression of lactose observed in some of the clinical cases reported by Rowntree and Fitz. Some light might be thrown upon this question if a form of experimental nephritis could be produced in which lactose excretion was suppressed. Until further evidence is obtained we must agree with Rowntree that the manner of lactose excretion is not completely understood.

Potassium Iodide. Frey[21] studied renal secretion by producing diuresis. He believed that the larger the amount of urine the nearer its composition would approach that of the glomerular excretion. He concluded from his experiments that the iodides are eliminated almost exclusively by the tubular epithelium.

Schlayer and Takayasu found that 0.025 gm. of potassium iodide injected intravenously into rabbits is completely eliminated in twenty-two to twenty-eight hours—average twenty-four hours. In experimental nephritis produced by chromate, sublimate, aloin, or uranium nitrate the iodide excretion is greatly delayed—forty to sixty hours. The excretion of potassium iodide may be greatly delayed, but it is never suppressed. The iodide is used by these authors as a test for the condition of the tubular epithelium, since they believe that it is excreted entirely by this part of the kidney tissue.

Von Monakow obtained indefinite results with potassium iodide. He does not regard it as a satisfactory test. In one of his clinical cases the autopsy revealed that nearly all the glomeruli were destroyed while the convoluted tubules showed only slight changes. In this case the iodide excretion was prolonged to one hundred and eighty hours. The prolongation of the excretion is much greater in this case than in those in which the lesions were mainly tubular.

Rowntree, Fitz, and Geraghty found that the excretion of potassium iodide is usually prolonged in chronic passive congestion of the kidney even in cases in which the phthalein output is normal.

Rowntree and Fitz found no constant relation between the degree of nephritis and the time of excretion of potassium iodide. They regard it, therefore, as of little value as a functional renal test.

Our tests were made by injecting 1 gm. of potassium iodide subcutaneously. Sandow's test was used for its detection in the urine. The time of elimination of this dose in four normal rabbits varied from 19.5 to 23.5 hours—average 21.5 hours.

In two rabbits in which phthalein excretion was permanently suppressed the elimination times for potassium iodide were 85.5

[21] Das Glomerulusprodukt ist ein Blutfiltrat, Arch. f. d. gesam. Physiologie. 1912, cxxxix, 435.

hours and ninety-five respectively. Both animals died the night following the disappearance of the iodide from the urine. At autopsy one showed a considerable amount of necrosis of the tubular epithelium; the other showed extensive granular degeneration, fatty metamorphosis, and some necrosis.

Another rabbit in which the phthalein excretion was completely suppressed was killed sixty-five hours after the iodide injection. The iodide was still being excreted. At autopsy the majority of the convoluted tubules were fouud necrotic and the others were fatty and granular. The glomeruli were all anatomically intact.

These experiments show that iodide excretion is delayed in tubular nephritis. Schlayer and Takayasu obtained similar results, but interpreted them to mean that the iodide is excreted by the tubular epithelium and not by the glomeruli. Apparently they believe that the functional capacity of the epithelium is decreased but not completely suppressed in tubular nephritis.

But no one has yet reported an instance of suppression of iodide excretion except in anuria; whereas phthalein, which is almost certainly excreted by the tubules, is suppressed when the injury of the epithelium passes beyond a certain degree. Unless we believe that degenerated epithelium incapable of excreting phthalein, indigocarmine, or methylene blue may still excrete iodide, we must admit that the glomeruli take part in the elimination of this substance. It seems more probable that the delayed excretion of iodide in our experiments is due to the fact that it must all be excreted by the glomeruli. Moderate injury of the glomeruli might further decrease the rate of excretion of iodide. The experimental results seem to us to afford good evidence that potassium iodide may be excreted by the glomeruli. The part that the tubular epithelium takes in the elimination of this substance is undetermined.

If we could produce experimentally a destruction of the glomeruli as complete as the destruction of the tubules in tartrate nephritis, valuable additional evidence could be obtained.

We have not made any functional tests with urea or sodium chloride. The discussion of these substances is therefore omitted.

Hemoglobin. This test was performed as follows: 5 c.c. of washed red blood cells from a rabbit were hemolyzed with distilled water, and after the addition of 0.5 per cent. sodium chlorid injected into the ear vein of the rabbit to be tested. In normal rabbits the urine is almost black three or four hours after this injection. Two rabbits with tartrate nephritis, causing complete suppression of phthalein, each gave a slightly colored urine after this test. The benzidene test for blood was strongly positive in these urines, but the color of the urine was very much less dark than in the normal. It is therefore probable that hemoglobin is excreted mainly by the convoluted tubules, but that a small amount may pass through the glomeruli.

SUMMARY. By subcutaneous injections of tartaric acid it is possible to produce in rabbits a form of acute nephritis in which the great majority of the convoluted tubules are necrotic and the rest fatty and granular. The glomeruli and collecting tubules may be anatomically intact.

In kidneys of the type just described the excretion of phenolsulphonephthalein, indigo-carmine, and methylene blue is completely suppressed. The excretion time of lactose is over twice as long as normal, while the excretion time of potassium iodide may be four times the normal. Both potassium iodide and lactose are excreted by this type of kidney.

The evidence obtained suggests that phthalein, indigo-carmine, and methylene blue are excreted exclusively by the convoluted tubules and that potassium iodide and lactose may be excreted by the glomeruli. Hemoglobin is excreted mainly by the tubules, but may pass through the glomeruli slowly.

A REPORT OF THE TREATMENT OF CEREBROSPINAL SYPHILIS BY INTRASPINOUS INJECTIONS OF SALVARSANIZED SERUM.[1]

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SINCE the discovery of the Wassermann reaction and the luetin tests, scientific proof has been added to the clinical belief that such affections as tabes and general paresis are not parasyphilitic diseases but true luetic processes.

The discovery of the Spirocheta pallida in these diseases by Noguchi and others not only adds further proof, but establishes the fact that they are active syphilitic affections. One of the things that created the belief that these affections were parasyphilitic diseases was their lack of response, in most instances, to antisyphilitic treatment. The cause, we now know, is due to the peculiarity of the choroid plexus of the dura mater, being more or less impermeable to such drugs as mercury, potassium iodide, and salvarsan. We must admit, however, that occasionally clinical improvement follows the administration of salvarsan, mercury, and potassium iodide given in the usual manner, but

[1] Read before the 116th Annual Meeting of the Medical and Chirurgical Faculty of Maryland, April 29, 1914.

improvement of the spinal fluid from the standpoint of the Wassermann reaction, cell count, globulin test, etc., is extremely rare, indicating that the improvement must be regarded only as temporary. When we further realize that even in the preëruptive stage of syphilis, while the blood still is negative to the Wassermann reaction, the spinal fluid may be positive, it is obvious that the proper method of handling these affections must be by direct applications to the nervous tissue itself. The difficulties that strew our path are not only technical but lie chiefly in the high susceptibility of the nervous tissue to foreign substances. However, that such a mode of attack is practicable has long been exemplified by intraspinous injections of serum in meningitis and tetanus. We have, too, the experience of several observers that even medicinal substances may be injected into the spinal canal without untoward effects.

Fortified by this knowledge and experience, various investigators have tried to improve syphilis of the nervous system by intraspinous injections of the newer antisyphilitic compounds. Salvarsan on account of its irritating alkaline content was out of the question. Wechselmann was the first to inject neosalvarsan in the spinal canal. Since that time Marinescu, Marie and Levaditi, Gennerich, and others have tried this treatment. Wechselmann used aqueous solutions, and after the injections it was found that the patients had violent reactions, consisting of severe headaches, vomiting, marked neuralgic pains in the legs, elevation of temperature, micturitional difficulties, etc. These severe reactive symptoms indicate an irritant action on the spinal cord, and on this account the method has not met with general favor.

Swift and Ellis tried injections of neosalvarsan solutions, but on account of the irritating action of the drug on the spinal cord gave them up and adopted their method of injecting salvarsanized serum. This method has found many adherents and is the method we have followed in our present study with some slight modification. The method of procedure is as follows: The patient is given a full dose of salvarsan intravenously; at the end of one hour 100 c.c. of blood is withdrawn. This blood is then sent to the laboratory. The next day the patient is prepared for the intraspinous injection of the salvarsanized serum by painting well the whole lumber and sacral regions with tincture of iodin. The patient may be sitting or lying, but it is essential that the back be well bowed. A point one-eighth to one-quarter inch to the right of the median line between the third and fourth lumbar intervertebral space is selected, and the needle, which is an ordinary lumbar puncture needle, is directed upward, inward, and forward. The successful entrance is indicated by the escape of spinal fluid. If the fluid is under great pressure an amount sufficient to reduce it is allowed to flow out, otherwise the same quan-

tity of fluid is withdrawn, as we have serum to inject (usually 15 to 30 c.c.). The injections are made by us with a syringe. Some use gravity, others combine both. The fluid is then sent to the laboratory for study. The patient is now sent to the ward and the foot of the bed elevated for two hours. He remains in bed until the temperature and pulse are normal. Some of the patients develop no reaction whatever, and they are allowed to go home the next morning. Others develop a meningismus, characterized by fever, increased pulse rate, nausea, vomiting, severe headaches, and shooting pains in the lower extremities. These symptoms are never alarming, and they pass off within twenty-four to forty-eight hours. Some of the patients feel comfortable so long as they are recumbent, but on standing develop a headache which may be quite severe. This condition lasts several days and then gradually subsides. We have not observed any unfavorable complications or sequelæ.

To date we have given twenty-nine intraspinous injections to 18 patients; 11 patients received one injection each; 4 received two injections each; 2 received three injections; and 1 received four injections. It is our plan, patients consenting, to repeat the injections every two or three weeks, irrespective of the clinical improvement, until the Wassermann reaction becomes negative in all dilutions, the cell count becomes normal, and there is negative globulin test. While some of our patients have shown a decided clinical progress, suggesting a cessation of treatment, the more accurate laboratory check has revealed the necessity of further injections.

At this point, the citation of a few cases from a clinical standpoint may be interesting.

B. F. C. entered hospital suffering with nausea, vomiting, and markedly defective mentality. Neurological examination, Wassermann test of the spinal fluid, etc., established the diagnosis of cerebrospinal lues. The Wassermann test of the blood was negative. Mercury and potassium iodide treatment ineffective. Twenty-four hours after the first intraspinous injection of salvarsanized serum his nausea and vomiting had disappeared and he became perfectly rational. Two weeks later he began again with nausea and vomiting, which was promptly relieved by the second intraspinous injection. He returned to his home in West Virginia feeling perfectly well. Patient returned to us February 9, 1914, feeling fine, having gained considerably in weight and being perfectly rational. He was then given another intraspinous injection.

J. H. A. Complaint: sharp pains in abdomen. At age of twenty-eight years, he had a chancre, followed by secondaries. He took mercury and potassium iodide for one year and was pronounced cured. Well until three years ago, when he began to notice weakness in limbs after walking up and down stairs.

Present Condition: Two years ago began to have sharp, intermittent pains in abdomen and difficulty in walking, until at the time of admission he was unable to walk at all. Examination lead to the diagnosis of tabes.

March 10, 1914. Intraspinous injection of 13 c.c. concentrated salvarsanized serum.

March 11. Patient had no more pains. Left the hospital March 14, 1914.

March 30. Again entered hospital. Given 0.6 gm. salvarsan intravenously, but on account of severe chill, lasting several hours, blood for intraspinous injection was not obtainable.

Again entered hospital April 7, 1914. Patient has no more pains; notices a steady improvement in his legs; 17 c.c. concentrated salvarsanized serum injected intraspinously. Patient, with slight support, walked from the bed-room to operating-room.

April 27. Patient feels fine. No pains; walks with perfect ease, but still notices a slight weakness which improves daily. Has resumed his occupation.

Case XI.—W. C. T. Complaint: violent headaches. Initial lesion October 1, 1913, followed by secondaries. Received four injections of salvarsan, and his symptoms promptly disappeared. Felt well until five weeks following last injection of salvarsan, when he began to have severe frontal headaches. Eye examination negative. Patient received another injection of salvarsan intravenously, which helped headaches for a few days, when they returned with increased severity. Hypodermic injections of biniodid in oil and large doses of potassium iodide proved unavailing.

March 7, 1914. Lumbar puncture made for diagnostic purposes. Fluid under pressure; Wassermann reaction of fluid triple plus; high cell count and positive globulin.

March 11, 1914. Headaches violent as ever, some nausea and vomiting, loss of weight and insomnia. Today 25 c.c. concentrated salvarsanized serum injected intraspinously. Forty-eight hours later, headaches had disappeared and have remained absent ever since. Patient's general condition has also shown marked improvement. Received another injection April 2, and another April 17.

Case VIII.—J. F. B. Initial lesion, 1894; left hemiplegia, 1911. Has received three injections of salvarsan intravenously. Symptoms complained of at time of treatment were scraping of right toe on floor and hemiplegia of right arm. Has received three intraspinous treatments. Now has good use of right arm and scraping of toe practically disappeared.

From a clinical review of our cases we have observed improvement, marked in some, slight in others, in practically every case, excepting one case of tabes in a patient who has been blind and paralyzed for many years, in whom the treatment was given

chiefly to satisfy the patient. We do not doubt that some of these patients may have been benefited by the older methods of treatment, but of this we are certain, that (1) the percentage of improvements would not have been as large, and (2) would not have been in most cases as prompt.

Though in certain respects the laboratory findings did not substantiate the clinical diagnosis of the cases included in this series, they in some cases established a definite diagnosis, often confirmed it, and in the latter event afforded evidence as to the efficiency of the treatment, either temporary or permanent, in the following directions:

1. As regards the globulin content of the cerebrospinal fluid.
2. As to the white blood cell count of the spinal fluid.
3. As to the Wassermann reaction of the blood.
4. As to the Wassermann reaction of the cerebrospinal fluid.

It is a source of great regret that this series did not include the colloidal gold test of Lange, but our work was already well advanced when the advisability of including this test was first seriously considered.

As regards the preparation of the salvarsanized serum the following procedure was employed:

The salvarsanized blood collected directly into centrifuge tubes of 50 c.c. capacity was kept at refrigerator temperature until the morning after collection (usually about sixteen to eighteen hours), when the clot was freed from the sides of the tube and the specimen centrifugalized until the serum was entirely free from cellular elements. Such cell-free serum was then transferred aseptically to other tubes. Except in the first few injections, when the sera were diluted to a 40 per cent. mixture with 0.9 per cent. sodium chloride solution, according to the method advicated by Ellis and Swift[2] we followed the plan employed by Boggs[3] of using undiluted serum. This has the advantage of decreasing the amount of fluid injected into the subdural space. We never experienced any ill effects attributable to this procedure, but rather feel that it is more efficacious and at the same time minimizes cord pressure symptoms. It was only by this means that we were enabled to institute the plan, which has been our recent custom, of giving the comparatively speaking huge doses of salvarsanized serum in the hope of securing a more intensive form of treatment than employed by others. The serum so prepared was inactivated in a water bath at 56° C. for thirty minutes, and when brought to body temperature was ready for administration.

Regarding the laboratory work carried on the following methods were employed: 1. In reference to the globulin content. For the sake of comformity to the method employed by others we used

[2] New York Med. Jour., 1912, xcvi, 53.

[3] Personal communication.

the Noguchi butyric acid test for globulin,[4] rather than at least more agreeable methods. Only such fluids as were entirely free from red corpuscles were utilized in this connection. A clear fluid without white precipitate either as sediment of in suspension was negative (—). An opacity of the entire specimen without any definite white precipitate either as sediment or in suspension was doubtful (±, ∓, or +). An opacity of the entire specimen with a definite white flocculant precipitate in suspension was definite (++). An opacity of the entire specimen with a coarse white flocculent precipitate as sediment and in suspension indicated a great increase (+++). The rapidity of development of the precipitate also influenced the intensity of the reaction, the most marked degree (++++) appearing immediately upon the addition of the alkali.

Globulin, though present in traces in all spinal fluid, is not detectable in normal amounts by the Noguchi method. Though increases occur occasionally in conditions other than central nervous syphilis which now definitely includes general paresis and tabes, its presence in increased quantities is usually associated with such involvement, the intensity of the reaction running roughly *pari passu* with the activity of the process.

2. With reference to the cell count. This estimate was made with a pipette and counting chamber in a manner comparable to that employed in counting the leukocytes of the blood, modified to suit the altered conditions encountered in the spinal fluid.

A cell count of more than eight white cells per cubic millimeter of undiluted spinal fluid was considered abnormal. Roughly corresponding to the activity and severity of a luetic involvement of the central nervous system this number is materially increased, the increase affecting the lymphocytic cell particularly, and the number varying from anywhere above eight to several hundred.

3. With reference to the Wassermann reaction of the blood. This reaction was performed substantially according to the technique which one of us has already described.[5] The exception is that in the majority of cases considered here we used two antigens, one Noguchi[6] antigen and the other a standard cholesterinized antigen.

The relative merits of these two antigens will be discussed by one of us[7] elsewhere.

Reaction of — and ± we consider diagnostically against lues (exclusive of cases involving the central nervous system when not

[4] For method see Noguchi, H., The Serum Diagnosis of Syphilis, first edition, page 118 to 119, Philadelphia, 1910.

[5] Judd, Charles C. W., Maryland Med. Jour., September, 1913, p. 220.

[6] Methods of preparation was essentially the same as that described by Kolmer and others. Arch. Int. Med., 1913, xii, 665, for Noguchi Antigen, and Sacks, H., Berlin klin. Woch., 1911, p. 2066, for the cholesterinized antigen.

[7] Judd, Charles C. W., Jour. Amer. Med. Assoc., July 25, 1914, lxiii.

infrequently the blood is negative and the spinal fluid if examined is found positive). Those cases designated as ∓ and + we consider has having an inconclusive reaction unless there is a revision downward from a positive reaction under the influence of treatment. Finally ++ and +++ are positive reactions and are diagnostic of lues.

4. With reference to the cerebrospinal fluid. The technique of the Wassermann was essentially the same as in the case of the blood, save that not possessing compliment it was not inactivated and, when feasible, smaller and greater concentrations of the fluid were utilized for each test. Selections as seemed most appropriate in the individual cases are made from the following: Undiluted fluid, diluted one in two parts, two in five, one in three, one in five, one in eight, and one in ten. By so doing small degrees of variation in fixative property were detected. In this connection we wish to emphasize the importance of as complete a titration of the spinal fluid as possible, as evidence of the actual influence of the treatment may thus be obtained which in our estimation is at least as important as the lowered cell count and diminished intensity of the Noguchi reaction which has been so heralded by others.

Certain of our cases, which presented clinical evidence of involvement of the central nervous system, in a known luetic, emphasize the probability that such disturbances are not necessarily due to organic implication of brain or cord in the luetic process, since the examination of the cerebrospinal fluid furnished altogether negative results while the blood Wassermann was positive. More probably this was due to some complicating condition, *e. g.*, arteriosclerosis. Our experience, however, is in accord with the suggestion of Bernstein,[8] to this extent at least, that in luetic patients presenting symptoms referable to the central nervous system, despite negative laboratory findings, an intraspinous injection of salvarsanized serum has done no harm and may be of incalculable prophylactic benefit.

Whether as a direct result of this treatment or not the laboratory findings in all of the cases included in this series which we have been enabled to follow have shown unequivocal improvement save in the question of the blood Wassermann. In the improvement there has been no particular uniformity with reference to any special one of these reactions. In no case, though as many as four injections have been administered, has there been a return from pathological conditions to absolute normality of the spinal fluid and blood in all phases of its examination, though in some of the cases there has been a restitution of the cerebrospinal fluid to normal in some respects. At best in well-established cases long

[8] Amer. Med. Assoc., 1914, lxii.

courses of treatment seem inevitable. Despite this the initial results are so far encouraging as to stimulate us to carry this treatment of these therapeutically discouraging cases to the limit in the hope of restoring not only the clinical condition of the patient but also both blood and spinal fluid to a normal condition in respect to all of these methods of examination.

CONCLUSIONS. 1. Intraspinous injection of salvarsanized serum, with proper precautions, is a safe treatment.

2. The results obtained indicate its superiority over the older known methods.

3. Treatment must be persisted in until the laboratory findings are negative irrespective of the clinical progress observed.

4. Such clinical and laboratory improvements as have been observed by us have still to go further. The permanancy of the improvement still has to be determined.

We wish to express our appreciation to Dr. Charles E. Simon for placing at our disposal the Wassermann reports of several of the cases herein included.

STUDIES IN THE CONCENTRATION OF BLOOD-SUGAR IN HEALTH AND DISEASE AS DETERMINED BY BANG'S MICRO-METHOD.[1]

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THIS work was stimulated by the current interest in the relation of blood-sugar to diabetes, nephritis, and conditions involving changes in the glands of internal secretion.

A brief outline may be cited of our present knowledge of the relation of blood-sugar to carbohydrate metabolism. The sugars and starches of the food, after conversion by the intestinal enzymes into glucose, etc. pass, by way of the portal circulation, to the liver, where the larger portion remains and is converted into glycogen.

Claude Bernard was the first to suggest the regulatory function of the liver in the sugar supply to the blood, it being warehoused in that organ and given to the muscles as demanded by their work.

[1] Aided by the J. Alison Scott Research Fund. Read before the Pathological Society of Philadelphia, October 8, 1914.

When he produced glycosuria by puncturing the floor of the fourth ventricle, he demonstrated the control of the nervous system over the output of sugar from the liver.

In animals, stimulation of sensory nerve trunks, and in human beings, lesions of the central nervous system produce the same phenomena.

Recent investigations reveal the importance of the ductless glands in the regulation of carbohydrate metabolism. Opie, MacCallum, and others consider that the islands of Langerhans furnish an internal secretion necessary for this metabolism, while Cushing concludes that the posterior lobe of the pituitary gland has an important influence on carbohydrate metabolism, in that any operative disturbance of it is followed by glycosuria and by lowering the assimilation limit of sugars. Increased tolerance follows a deficiency in secretion on the removal of this portion of the gland.

Experimentally, the influence of adrenalin is well established, though clinically there is no organic disease of the adrenals which produces glycosuria or diabetes.

Disregarding further theories concerning glycogenesis and glycolysis, it may be borne in mind that glucose is the principle sugar of the blood, that it is "a food material in transport from the organs of supply to the organs of consumption," and finally that its concentration in normal individuals varies between 0.06 per cent. and 0.11 per cent., it being generally conceded that 0.085 per cent. is the average.

Conditions Causing Variations in Blood-sugar Concentration. Hyperglycemia and glycosuria are the result of a disturbance in equilibrium of that delicate chemical or nervous mechanism which controls the sugar supply from the various glycogen depots. Conditions causing an increase in blood-sugar may be:

Physiological, as alimentary changes, nervous or emotional disturbances, pregnancy and infancy, etc.

Pathological, as diabetes, conditions involving changes in glands of internal secretion, pancreatic and certain hepatic diseases, cerebral injury, tumor or hemorrhage, and finally peripheral nerve diseases.

Experimental, as renal diabetes with intoxication by means of metallic salts, stimulation of splanchnics, asphyxia, and drugs, as adrenalin, diuretics, morphin, strychnin, chloroform, etc.

Total reduction in blood-sugar is less common than hyperglycemia occurring chiefly in exhaustion and phloridzin glycosuria.

The Micro-method of Sugar Determination. Bang[2] introduced this method in his monograph *Der Blutzucker*, in January, 1913, and in November of the same year so modified it as greatly to enhance its value as a rapid bedside method.

[2] Bioch. Ztschr., November, 1913, H. 4, B. 57.

TECHNIQUE. Two or three drops of blood, approximately 100 mg. from a prick in the finger, are taken up on a small, specially prepared, and weighed piece of filter paper. The paper with its contained blood is again weighed, the amount of blood thus being accurately estimated. Next the paper is dropped into a test-tube containing 6.5 c.c. of an alkaline potassium chloride solution which has been brought to the boiling-point, and is allowed to remain there for a half-hour, during which time the albumin coagulates and remains in the paper while the sugar diffuses into the solution. The solution is then poured into a small flask, another 6.5 c.c. of the alkaline solution is poured in the original test-tube, thus washing the remaining sugar from the paper. This is then added to that in the flask with 1 c.c. of a specially prepared copper solution. The mixture is brought to a boil by heating for exactly one and a half minutes and boiled for two minutes. When cool a few drops of a specially prepared starch solution is added as an indicator and titrated with $\frac{n}{100}$ iodin solution until the blue iodin starch color reaction appears and persists for a half-minute. The theoretical consideration and the details of the technique are given in Bang's paper.

The small amount of blood required, the ready means of collecting it, the opportunity for repeated and serial estimations without discomfort to the patient, and finally the rapidity and simplicity of the method, afford advantages far greater than any of the older methods.

Though quite new the method has been used by a number of workers, all of whom confirm Bang's findings (Hirsch and Reinbach,[3] Tannhauser and Pfitzer,[4] Jacobson,[5] Leire,[6] Bing,[7] etc.). The test has been successfully controlled by the methods of Fehling, Knapp, Bertrand, Michaelis, and Rona, and we have controlled it with Allihn's method, and with known sugar solutions, with satisfactory results.

My results show that the concentration of sugar in normal cases varies between 0.065 per cent. and 0.1 per cent. In each test two samples were taken, the average of the two being the given result.

STUDIES IN ALIMENTARY HYPERGLYCEMIA. Comparatively little work has been done to date in this line. The factors which govern the various stages in the breakdown of sugar may vary considerably in different animal species, hence the results are of greatest value when obtained directly in man.

Much more work has been done in alimenary glycosuria, concerning which Allen[8] states that the results "may be obscured by imper-

[3] Hoppe Seyler's Ztschr. f. Phys. Chem., 1913, Bd. 87, H. 2, S. 122–141.
[4] Münch. med. Woch., 1913, ix, S. 2155.
[5] Biochem. Ztschr., Bd. 56, H. $\frac{3}{6}$, S. 471–494.
[6] Der Blutzucker, Wiesbaden, 1913.
[7] Deutsch. Arch. f. klin. Med., 1914, Bd. 113, H. $\frac{3}{4}$.
[8] Glycosuria and Diabetes, Boston, 1913.

meability of the kidney, and even in diabetes, when renal involvement exists, the reaction may be negative, the sugar merely heaping up in the blood. For this reason examination of the blood is most important to accompany or replace examination of the urine, and the most recent studies concerning lowered assimilation of sugar are based not upon alimentary glycosuria but upon alimentary hyperglycemia."

The most characteristic sign of a disturbance in carbohydrate metabolism is the increase in the sugar content of the blood. The value of the alimenary test is greater than an occasional single test for preformed sugar in that the former, or serial test, may reveal such a disturbance far earlier.

The rapidity of absorption may be controlled by the type of starch, some forms being absorbed much more quickly than others, and by the addition of fat which retards absorption. The rate of progress from the stomach to the intestine is important, the tolerance of ingested sugar being almost doubled by an accompanying meal.

Tachau[9] found only a very slight increase in normal cases after 100 grams of glucose, that amount being recognized as the standard quantity. The lack of uniform results by various workers is striking, a few having failed to get any positive results. There are several factors responsible for this, the most prominent of which are variations in individual reactions, and that the rise in normal cases frequently occurs within a half-hour after oral administration, and by the end of the hour has resumed the normal or almost normal level.

Again, all work done prior to the introduction of Bang's method last year involved the use of much more blood, and consequently but one or occasionally two tests were made in each case. Naturally the conclusions drawn from such limited series are lacking in uniformity and contribute more to the confusion than to the elucidation of a complex subject.

Alimentary Hyperglycemia in Normal Cases. In order to ascertain the degree of fluctuation of the concentration of sugar in the blood, lying within the physiological boundaries, a series of normal cases was studied.

In these tests 100 grams of glucose dissolved in 420 c.c. of water was given before breakfast. Estimations of blood-sugar were then made at frequent intervals, as shown in Table I.

This table illustrates the irregularity in time at which the height of the curve is reached, which may be from a half to two hours. In some cases the normal level may be resumed within one hour. The difference in degree of the individual reaction is also worthy of note. Case 3 was the only one which failed to show a definite rise

[9] Arch. f. klin. Med., 1911, 104, S. 437–447.

in sugar concentration. Case 9 received 20 grams of glucose subcutaneously and no rise occurred until four and a half hours after the injection.[10]

TABLE I.—ALIMENTARY HYPERGLYCEMIA IN HEALTH.

Case.	1, S.R.	2, S.H.	3, B.	4, J.	5, H.	6, Sa.	7, D.	8, L.	9, N.
Preformed Sugar.	0,099	0,108	0,100	0,078	0,075	0,097	0,101	0,065	0,074.
100 gms. glucose.	..	..	..	..	..	..	..	..	20 gms. subcutaneously.
½ hour.	..	..	0,112	0,111	0,149	0,126	0,142	0,143	0,074
1 "	0,127	0,110	0,102	0,106	0,103	0,142	0,108	0,147	
1½ "	..	..	0,108	0,138	0,093	0,115	0,112	..	0,073
2 "	0,141	0,157	..	..	..	..	0,074	0,141	
2½ "	..	..	0,087	0,127	0,099	0,073	..	..	0,058
3 "	..	..	..	..	..	..	0,072	0,123	
3½ "	..	..	0,105	0,091	0,082	0,091			
4 "	..	..	..	..	..	..	..	0,092	
4½ "	..	..	0,084	..	0,076	0,066	0,085	..	0,101
5 "									
5½ "	..	..	..	..	..	..	..	..	0,091
6 "	..	..	0,109	..	..	..	..	..	0,105

So far my findings partially confirm those of Jacobson,[11] who recently published his series of normal cases studied by the same method, in which he found a rise in blood-sugar within five minutes after 100 grams of glucose, the height being reached in a half-hour and the preformed level resumed in approximately two hours.

DIABETES. The most characteristic symptom of this disturbance in carbohydrate metabolism is the increase in the sugar content of the blood.

It is of importance to distinguish between the glycosuria of febrile, toxic, hepatic, or nervous diseases and that of early diabetes, especially when it is borne in mind that a diabetes may be the result of any of the above-mentioned causes of a transient glycosuria. Hyperglycemia may exist for a variable length of time before there is any evidence of sugar in the urine, hence an earlier and more reliable criterion of diabetes is the study of the blood-sugar. In early diabetes, postprandial hyperglycemia is greater and longer in duration than in health, and becomes progressively more lasting until there are no low levels reached in the course of the day, the result of this slow decline being the early stage of a true diabetes. Finally the barriers give way, sugar overflows into the urine, and the disease is well established. For a time the blood-sugar level may remain fairly constant, only to rise again when the toxic effect of the excess of sugar renders the kidneys less permeable to it[12] (Macleod).

Using Bang's method in their recent experiment with intravenous injections of sugar solution, Tannhauser and Pfitzer[13] found that in

[10] A 5 per cent. solution was injected into the thigh, but owing to the pain and discomfort the test was not repeated.

[11] Biochem. Ztschr., Bd. 56, H. $\frac{5}{6}$, S. 471–494.

[12] Jour. Amer. Med. Assoc., vol. lxii, No. 16, p. 1222.

[13] Münch. med. Woch., 1913, ix, 2155.

diabetes the blood-sugar was markedly increased and remained so for hours, there being an accompanying parallel increase in glycosuria

ALIMENTARY HYPERGLYCEMIA IN DIABETES. Alimentary hyperglycemia was studied in a series of cases of diabetes. Here the method of adminsitration and technique were the same as those used for the normal cases.

TABLE II.—ALIMENTARY HYPERGLYCEMIA IN DIABETES.

Case.	1, K.	2, A.	3, D.S.	4, F.	5, P.H.	6, M.	7, S.	8, P.	9, C.	1, K.
Preformed sugar.	0,217	0,192	0,152	0,251	0,306	0,229	0,234	0,243	0,235	0,190
100 gms. glucose.	..	..	..	..	..	..	..	..	..	100 gms. glucose by rectum.
½ hour	..	..	0,226	0,353	0,398	0,372	0,350	0,328	0,267	
1 "	0,365	0,270	0,261	0,355	0,389	0,377	0,348	0,402	0,333	0,182
1½ "	..	..	0,299	0,378	0,343	0,392	0,372	..	0,392	
2 "	0,344	0,370	..	0,429	..	0,325	0,437	0,448	..	0,196
2½ "	..	..	0,265	..	0,359					
3 "	..	..	..	..	..	0,240	0,429	0,503	0,457	0,196
3½ "	..	..	0,216	..	0,319					
4 "	..	..	..	..	..	0,252	0,324	0,467	..	0,269
4½ "	..	..	..	..	0,318					
5 "	..	..	..	..	..	..	..	..	..	0,233
6 "	..	..	..	0,253						

From this table it will be observed that alimentary hyperglycemia is very pronounced, the height of the level appearing at any time from one-half to three hours after the ingestion of glucose, and the duration being greatly prolonged.

In Case 1 it is interesting to note the delay and impairment of absorption when the glucose was administered by rectum.

No marked rise occurred for four hours after the rectal injection. The preformed value was lower here, as the patient had been on a carbohydrate-free diet for ten days. Several patients were unable to retain the glucose solution by rectum, and therefore a larger series is not presented.

ALIMENTARY HYPERGLYCEMIA IN VARIOUS DISEASES. These cases were observed as each presented a condition in which a disturbance in carbohydrate metabolism might be suspected if the most recent theories on the subject of sugar regulation are to be accepted. The technique was the same as in the former series.

Table III shows especially interesting results in the pancreatic and pituitary cases. In Case 2 a series of tests were carried out, the first after 100 grams of glucose, the second after 167 grams of bread, representing approximately 100 grams of glucose. In the latter series it will be observed that the rise in blood-sugar was less pronounced and slower than where glucose was given.[14]

[14] At the end of a half-hour the patient was given cocain as a local anesthetic for a slight surgical operation, and this was followed by a definite hyperglycemia.

TABLE III.—ALIMENTARY HYPERGLYCEMIA IN VARIOUS DISEASES.

Case	1, O'B.		2, D. S.		D. S.		3, R. S.		4, Mr. McM.		5, H. C.		6, Miss McM.		7, Sh.		8, My.		9, J. T.		10, E. J.
Diagnosis	Hepatic cirrhosis.	Glycosuria.	Hepatic cirrhosis.	Glycosuria.	Same as case 2.	Glycosuria.	Sub-acute pancreatitis.	Glycosuria.	Pancreatitis.	Glycosuria.	Acromegaly (?).	Glycosuria.	Optic neuritis. Pituitary (?)	Glycosuria.	Tabes (?).	Glycosuria.	Endocarditis.	Glycosuria.	Plumbism.	Glycosuria.	Infantilism. Pituitary (?)
Preformed sugar.	0.081	..	0.072	..	0.108	..	0.066	..	0.093	..	0.104	..	0.078	..	0.078	..	0.125	..	0.086	−	0.085
100 gm. glucose.	...	..	...	..	167 gms. bread.																
½ hour.	0.138	..	0.166	..	0.112	−	0.180	..	0.183	Dec.	0.120	−	0.136	−	0.180	−	0.211	−	0.149	+	0.185
1 "	0.160	..	0.167	..	0.147	−	0.178	..	0.193	+	0.172	−	0.217	Dec.	0.218	+	0.149	−	0.249	++	0.137
1½ "	0.137	..	0.207	..	..	..	0.238	..	0.173	++	0.151	−	0.217	+	0.320	+	0.141	−	0.217	++	
2 "	...	..	...	..	...	..	...	..	0.108	+	...	−	...	..	...	..	...	..	...	..	0.133
2½ "	...	..	...	..	0.128	−	...	..	...	..	0.130	−	...	..	...	..	...	..	...	..	0.142
3 "	...	..	0.206	..	...	..	0.183	..	...	..	...	..	0.073	−	0.164	..	0.157	−	0.130	..	
3½ "	0.141	..	...	..	...	..	0.132	..	0.074	Dec.											0.099
4 "	...	..	...	..	0.085	−	...	..	...	..	0.088	−	...	..	...	..	...	..	...	..	
4½ "	...	..	...	..	...	..	...	..	0.079	−											

In 7 of the cases, repeated analyses were made for glycosuria, the results of which are similar to those of other workers in that there is no constant level of hyperglycemia at which sugar appears in the urine.

The height of the curve was reached in the majority of these cases in from one to one and one-half hours, the duration of the hyperglycemia lying between that of the normal and the diabetic.

NEPHRITIS. The following cases were studied owing to the theoretical interest as well as the existing diversity of opinion in regard to blood-sugar values in high tension nephritis. The first observations of a rise in blood-sugar with renal involvement were those of Neubauer, confirmation of which has been furnished by Frank,[15] Leire,[16] Weiland,[17] Rolly and Opperman,[18] and many others.

Neubauer[19] considers an existing relation between increased blood-pressure and hyperglycemia, while others attribute the latter to such causes as uremia, edema with chloride retention, dyspnea, etc.

Bing and Jacobson[20] recently found a slight increase in such cases on admission to the hospital, the tendency being to fall as the stay in the hospital continued.

The following tests were made to ascertain the possible relationship between blood-sugar, blood-pressure, phthalein elimination, congested liver, and edema. Table IV.

This short series of 26 cases is presented merely as a preliminary report. It will be seen that of the 16 cases with a blood-pressure ranging from 180 to 280 the blood-sugar values lay within normal limits in but 5 cases, while the 11 other cases showed a definite, though moderate, hyperglycemia.

In 11 of these 16 cases the phthalein elimination was reduced. The influence of chronic passive congestion upon the phthalein output must be taken into consideration.

In 10 other cases without high pressure, 7 were normal and 3 were hyperglycemic. Of the 19 cases showing a low phthalein elimination, 9 showed a definite rise in blood-sugar.

Where edema was present it has been noted and its presence reveals no association with the blood-sugar level. An enlarged and congested liver might be expected to be the source of some alteration in carbohydrate metabolism, but in the tests for the preformed sugar alone, *i. e.*, not including the alimentary test, the expectations are not borne out.

[15] Deutsch. Arch. f. klin. Med., 1911, p. 103, S. 397.
[16] Der Blutzucker, Wiesbaden, 1913.
[17] Zentralbl. f. d. ges. Phys. u. Path. d. Stoffwechsels, 1910, Nr. 13.
[18] Ztschr. f. phys. Chem., 1913, Bd. 88., H. 2, S. 155–158.
[19] Biochem. Ztschr. 25, 1910, S. 284–295; Arch. f. exp. Path. u. Pharm., 1911–12, p. 67, S. 192–193.
[20] Deutsch. Arch. f. klin. Med., 1914, Bd. 113, H. $\frac{5}{6}$.

TABLE IV.—NEPHRITIS, SHOWING RELATION OF BLOOD-SUGAR TO BLOOD-PRESSURE, PHTHALEIN ELIMINATION, ETC.

Case.	Age.	Diagnosis.	Daet.	Blood-sugar.	Blood-pressure.	Phthalein, per cent.	Liver.	Notes.
1 J. B.	39	Cardiorenal.	April 1	0.135	130–60	10	9 cm.*	Four and a half hours after food. Early A.M. Edema.
			April 2	0.073	110–60			
2 J. H.	34	Chronic interstitial nephritis; chronic myocarditis.	April 1	0.060	190–130	40	5 cm.	Edema.
			April 2	0.087				
3 J. M.	48	Cardiorenal.	April 1	0.076	135–98	40	8 cm.	Edema.
			May 22	0.090	155–85			
4 J. W.	45	Chronic nephritis; chronic myocarditis.	April 1	0.090	145–85	45	4 cm.	Edema.
					155–85			
5 N. P.	65	Chronic interstitial nephritis; arteriosclerosis.	April 1	0.121	180–130	35	Negative	Three hours after food.
6 D.	..	Chronic interstitial nephritis; arteriosclerosis; arthritis.	April 7	0.106	200–170			
7 J. J.	56	Chronic interstitial nephritis; arthritis.	April 15	0.132	180–90	—	3 cm.	Four hours after food.
					150–90			
			April 16	0.076	150–90	—		
8 M. G.	54	Chronic interstitial nephritis; endocarditis.	April 30	0.114	190–110		5 cm.	
9 M. W.	28	Chronic interstitial nephritis.	May 2	0.125	262–175	10	Negative.	Gastro-intestinal symptoms; edema; headache.
					225–			
			June 16	0.123	256–163	3		
10 A. P.	49	Chronic nephritis; chronic myocarditis.	May 5	0.159	180–100	15	4.5 cm.	Edema.
11 H. L.	75	Chronic interstitial nephritis (vascular); arterio-sclerosis.	May 5	0.131	160–95	30	5 cm.	
			May 12	0.119	145–85			
			June 4		135–95	29		
12 A. S.	22	Acute nephritis.	May 22	0.095	146–90	36	Negative.	Edema.
13 H. H.	52	Chronic interstitial nephritis.	Mar. 23	0.081	150–125	36	1 cm.	Edema.
					120–80			
			April 2	0.073	120–80			
14 A. W.	70	Chronic nephritis; chronic myocarditis.	Feb. 18	0.161	135–85	—	10 cm.	Edema.
15 G. B.	..	Chronic interstitial nephritis.	Feb. 25	0.082				
			Mar. 9	0.075				
16 C. B.	40	Chronic interstitial nephritis; renal.	Jan. 30	0.146	250–150	14	2 cm.	Headache intense.
			Feb. 14	0.152				
17 C. E.	50	Chronic interstitial nephritis; cerebral hemorrhage; arteriosclerosis.	Mar. 21	0.111	210–100	—	Cloudy. Swollen.	Death same day.
					160–95			
18 J. S.	47	Hypertension.	Mar. 21	0.117	180–130	55	Negative.	
					140–100			
19 L. L.	55	Chronic interstitial nephritis (vascular).	Mar. 23	0.082	225–115	43	Negative.	
			April 2	0.077	160–85			
20 M. C.	41	Chronic interstitial nephritis; chronic myocarditis.	Mar. 30	0.090	152–100	8.5	6 cm.	Edema.
21 L. R.	56	Chronic interstitial nephritis; hypertension.	May 29	0.137	280–	53	1 cm.	
					220–110			
22 E.O.D.	15	Acute nephritis.	May 29	0.122	126–82	30	9 cm.	Edema.
23 S. R.	26	Chronic interstitail nephritis.	June 16	0.121	230–150	22	Negative.	
24 M. R.	27	Chronic interstitial nephritis; hypertension.	June 16	0.117	225–180			
25 P.F.	61	Chronic interstitial nephritis.	June 4	0.074	170–130	24	9.5 cm.	Edema.
					190–110			
26 M. L.	54	Chronic interstitial nephritis; uremia.	Sept. 26	0.127	202–135	67	Negative.	

* Below costal border in midclavicular line.

ALIMENTARY HYPERGLYCEMIA IN NEPHRITIS. Consider, however, the following table in which nephritics were fed 100 grams of glucose:

TABLE V.—ALIMENTARY HYPERGLYCEMIA IN NEPHRITIS.

Case.	1, H.L.	2, J.H.	3, S.R.	4, H.P.
Diagnosis.	Chr. int. neph.	Chr. int. neph.	Ac. par. neph.	Chr. int. neph.
Preformed sugar.	0.119	0.085	0.095	0.074
100 gms. glucose.				
½ hour.	0.200	..	0.179	0.118
1 "	0.172	0.176	..	0.126
1½ "	..	0.218	0.220	
2 "	..	0.161	0.159	0.148
2½ "	0.177			
3 "	..	0.097	0.124	0.114
3½ "	..	..	0.126	
4 "	0.104			
Edema.	—	+	+	+
Enlarged liver.	5 cm.	5 cm.	—	9.5 cm.

In each case the urine was tested for sugar at one-hour intervals, with negative results throughout.

These results emphasize in the individual cases the existence of normal preformed values associated with markedly abnormal values in alimentary hyperglycemia, as do the results in Tables II and III.

Aside from impaired renal function we have to consider altered hepatic function as well as the existence of pancreatitis in a certain proportion of elderly cases. In all cases the rapidity of passage from the stomach to the intestine and rapidity of absorption add somewhat to the uncertainty of the results.

More detailed studies are being carried on in association with Dr. Jonas, in which, in a series of high-pressure cases, the blood-nitrogen and blood-sugar are being studied simultaneously after definite periods of various types of feeding. Chloride retention, blood-pressure, and phthalein elimination with other factors are also being considered.

PNEUMONIA. In studying the blood-sugar in this series of 17 cases of pneumonia the possible influence of blood-pressure, temperature, and renal changes was observed as well as the associated leukocytosis. Table VI.

In 8 cases hyperglycemia was present, being accompanied by fever in all but 2; 5 of the remaining 7 were convalescent and had no fever.

There was apparently no relation between the blood-sugar values on the one hand and blood-pressure, leukocytosis, and renal involvement on the other, a feature well illustrated by Case 7, which was followed closely from the fifth day to the crisis.

TABLE VI.—BLOOD-SUGAR IN PNEUMONIA.

Case.	Age.	Date.	Diagnosis.	Day of disease.	Blood-sugar.	Blood-pressure.	Temper-ature.	Leuko-cytes.	Notes.
1, J.	..	April 7	Lobar pneumonia	8th	0.091	115–65	98.2°	9,600	Crisis
2, M. O'D.	23	April 4	Lobar pneumonia	4th	0.119	155–100	100.2°	23,200	Death next day.
3, D. R.	18	April 4	Lobar pneumonia	23d	0.090	125–65	98.2°	20,000	Convalescent. Leukocytes taken 4 days previous.
4, A. S.	22	April 4	Lobar pneumonia	8th	0.114	140–105	97.4°	8,600	Convalescent.
5, B. J.	70	April 4	Lobar pneumonia	9th	0.158	130–100	98.2°	11,800	Convalescent.
6, A. M.	27	April 9	Articular rheumatism; broncho-pneumonia; endocarditis	2d	0.106	115–56	101.2°	9,000	
7, J. M.	34	April 9	Lobar pneumonia	5th	0.138	100–60	102.0°	13,600	Extreme cyanosis.
7, J. M.	34	April 11	Lobar pneumonia	7th	0.139	90–60	102.0°		
7, J. M.	34	April 12	Lobar pneumonia	8th	0.138	80–50	101.0°	28,000	
7, J. M.	34	April 13	Lobar pneumonia	9th	0.084	100–65	100.0°	35,000	Crisis.
8, C. L.	37	April 11	Bronchopneumonia	7th	0.091	—	103.2°	17,500	
9, B. L.	24	April 11	Lobar pneumonia	2d	0.137	—	102.3°	14,300	
10, C. F.	45	April 11	Lobar pneumonia	6th	0.122	116–96	101.0°	16,800	
11, B. McD.	65	April 11	Lobar pneumonia	10th	0.156	140–85	101.0°	9,600	Death.
12, M. H.	30	April 11	Lobar pneumonia	11th	0.086	135–85	97.2°	24,200	Convalescent.
13, P. B.	13	April 11	Lobar pneumonia; empyema	23d	0.093	125–85	97.0°	24,000	Empyema. Pneumonia subsided.
14, H. McC.	14	April 11	Bronchopneumonia; arthritis	5th	0.093	90–60	102.1°	12,900	
15, C. S.	32	April 4	Lobar pneumonia; empyema	14th	0.092	110–85	98.0°	19,800	Pneumonia subsided. Empyema.
16 N. F.	51	April 30	Pneumonia; endocarditis	9th	0.100	135–75	101.2°	21,000	
17, B. N.	52	May 26	Lobar pneumonia	9th	0.113	115–82	103.4°	19,700	Death.

VARIOUS DISEASES. The micro method was used in the study of blood-sugar values in a series of 64 miscellaneous cases as follows:

TABLE VII.

Case No.	Diagnosis.	Blood-sugar.
1	Pancreatic diseases	0.066
2	" "	0.093
3	" "	0.119
4	" "	0.081
1	Apoplexy	0.182
2	"	0.118
3	"	0.125
4	"	0.126
1	Primary anemia	0.134
2[22]	" "	0.061
2	" "	0.070
1	Leukemia	0.103
1	Erysipelas	0.155
2	"	0.089
3	"	0.084
4	"	0.104
1	Carcinoma	0.171
2	"	0.181
3	"	0.095
4	"	0.102
5	"	0.111
6	"	0.074
1	Acute articular rheumatism	0.061
2	" " "	0.091
3	" " "	0.106
4	" " "	0.118
1	Hyperthyroidism	0.082
1	"	0.067
1	"	0.080
2	"	0.140
2	"	0.093
2	"	0.108
3	"	0.070
1	Exophthalmic goitre; endocarditis	0.170
1	Typhoid	0.147
2	"	0.122
3	"	0.103
4	"	0.103
5	"	0.105
6	"	0.117
1	Pulmonary tuberculosis	0.074
2	" "	0.087
3	" "	0.094
4	" "	0.141
4	" "	0.116
4	" "	0.135
5	" "	0.139
6	" "	0.100
7	" "	0.103
8	Tuberculous peritonitis	0.115
9	Acute miliary tuberculosis	0.125
10	Tuberculous meningitis	0.127
10	" "	0.091
11	" "	0.080
12	" "	0.117

[22] Where the case numbers are repeated, the tests have been made at various stages of the disease.

TABLE VII—Continued.

Case No.	Diagnosis.	Blood-sugar.
13	Tuberculous meningitis	0.139
13	" "	0.171
14	" "	0.116
1	Neurosis	0.099
1	Tonsillitis	0.075
2	"	0.061
1	Chorea	0.101
1	Epilepsy	0.100
1	"	0.118
1	Hysteria	0.111
1	Psoriasis	0.078
1	Plumbism	0.086
1	Chronic jaundice	0.061
1	Pituitary disease	0.117
2	" "	0.116
3	" "	0.104
4	" "	0.078
5	" "	0.085
6	" "	0.110

Thus it will be seen that hyperglycemia was present in all the cases of apoplexy and typhoid and in 3 out of 6 cases of cancer.

In 14 cases of tuberculosis it was present in 8, being especially pronounced in those having fever or involvement of the meninges.

In nervous diseases, values along the upper normal limit were the usual findings.

CONCLUSIONS. 1. In health a moderate rise in blood-sugar (0.14 per cent. to 0.15 per cent.) occurs after feeding 100 grams of glucose, reaching its height in from one-half to two hours and quickly subsiding.

2. There is no constant blood-sugar level at which sugar appears in the urine.

3. Evidently absorption after rectal and subcutaneous injection is slower than after feeding by mouth, however, owing to the discomfort produced by the former methods this series is too limited to permit of definite conclusions in regard to this point.

4. Where a disturbance in carbohydrate metabolism exists there may be a normal sugar concentration associated with a most pronounced alimentary hyperglycemia.

5. In diabetes, alimentary hyperglycemia is pronounced, the height of the sugar level appearing at any time from one-half to three hours after the ingestion of glucose, and the duration being more prolonged than in other conditions.

6. Pancreatic, nephritic, and pituitary cases all furnish very high figures after feeding glucose, the duration lying between that of normal and of diabetic patients.

7. A moderate hyperglycemia occurs in many high-pressure nephritic cases, and frequently in those with low phthalein elimination. In most cases of nephritis without high-pressure the blood-sugar is normal. Edema and hepatic congestion do not influence

blood-sugar values, though the role they may play in alimentary hyperglycemia, which is pronounced in nephritis, I am at this time not prepared to say.

8. A rise in blood-sugar occurs in pneumonia and may be present in the absence of fever. It is apparently uninfluenced by blood-pressure, leukocytosis, or renal involvement.

9. Hyperglycemia occurs quite constantly in apoplexy, typhoid, and tuberculosis in the presence of fever and in some cases of cancer.

10. The test, owing to its simplicity and accuracy, affords a practical method for early diagnosis and control of dietary therapeusis.

I wish to express my appreciation of the kind assistance given by Dr. A. I. Ringer in the perfecting of the technique of this method and to Dr. Morris J. Lewis for the opportunity to study some of the pneumonia patients who were on his service in the Pennsylvania Hospital.

All the other cases were from the wards of the University Hospital on the service of Dr. Alfred Stengel.

EXTRAPHYSIOLOGICAL OR PUTREFACTIVE UREA.

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Schematically considered, the destruction of nitrogenous foodstuffs in the animal body end in the formation of the two principal and characteristic organic constituents of the urine, urea and uric acid. Neither, nevertheless, represent the last residue of the gradual disintegration of nitrogenous substances; they originate, on the contrary, through a synthetic process performed principally by the liver from ammonia, which may be considered as the most simple residue of the nitrogenous katabolism. In birds and reptiles the ammonia gives rise to uric acid, and in man and mammalians to urea. The small proportion of uric acid found in the urine of the latter proceeds from a real process of gradual dissociation of nucleins. These substances are disintegrated until xanthic bases result, which, by means of enzymatic oxidation, are turned into uric acid. While in birds and reptiles the introduced urea turns, in its greatest part, into uric acid, in mammalian animals certain enzymes which exist in various organs (Schittenhelm's uricolytic ferments) tend to destroy the uric acid, changing it into urea. Though apparently opposite it is probable that both compounds may proceed in each case from the same physiological process.

How does urea originate from ammonia? This is not entirely

known, but the principal explanation of this biological fact is to be found in the Nencki-Schultze-Schmideberg anhydration theory and in the Hofmeister oxidation theory; both theories suppose the preëxistence of ammonia. It is not well fixed, at present, what part of the truth corresponds to each one of these theories. It is not known also if there are other organs besides the liver which may produce the urea from ammoniacal compounds. Especially interesting is the formation of urea from arginin; here, 50 per cent. of the nitrogen of this substance is directly dissociated by a ferment which has been isolated from the liver, kidneys, thymus, and other lymphatic glands.

The following conclusions can be accepted as well-established facts: (1) the urea proceeds in the body from ammoniacal compounds; (2) the liver is the only organ for which the formation of urea has been experimentally proved; (3) the urea may derivate also from dissociation of other nitrogenous compounds, as, for example, arginin.

Though all nitrogenous foodstuffs which are decomposed in a given animal do not give rise, however, to the production of urea, this principle may be considered as the main nitrogenous product of tissue katabolism, at least in man and mammalians, and therefore it is a substance entirely physiological to the animal body.

In the present article I will endeavor to expose the experimental basis upon which it is possible to establish that, in the common conditions of human life, a part of the urea, as small as it may be, proceeds directly from the intestinal putrefaction; that is to say, it is the product of chemical transformations which takes place outside of the normal tissue katabolism. This part of the urinary urea must receive the name of extraphysiological or *putrefactive* urea. In the sick man, especially in the diabetic, the putrefactive urea increases enormously and plays an essential part in the pathogeny of the malady.

If a solution of an ammoniacal salt of a volatile or inferior fatty acid is introduced into the rectum and its entire absorption permitted the result to be observed is that the twenty-four hours, amount of urea increases. This hyperexcretion of urea is accompanied by two interesting phenomena when butyrate of ammonia is the employed salt. The twenty-four hours' urinary volume increases (polyuria) and the excreted acetone greatly augments upon the normal proportions (acetonuria). If the rectal injections are continued for many days the polyuria and the acetonuria reach a high degree.

One of the experiments has been carried out on a subject specially selected in order that the pharmacological influence of the salt could reach the strongest effect with the least quantity used. The person referred to is a female, weighs 45 kilos, lives in the tropical and Atlantic region (Caracas, Venezuela), and is submitted to a

uniform vegetarian diet very poor in nitrogen. The experiment has been divided into two series: the first series has been preceded by a preparatory period of the same diet. During the second series rectal injections of a watery solution of butyrate of ammonia have been used: 50 c.c. the first two days, 75 c.c. the two following, and 100 c.c. the rest of the series. The proportion of ammonia is exactly determined (3.825 grams NH_3 for 100 c.c.) and pure butyric acid (19.8 $C_4H_8O_2$ for 100 c.c.) is added until neutralization takes place; the rosolic acid has been employed as indicator. The daily quantity is diluted four or five times with water and fractionally injected. The quantitative estimation of the various urinary elements has been made as accurately as possible, employing the most reliable methods. The urinary volume has been determined by weight and density, the pipettes and flasks being graduated at the laboratory temperature (24° C.). For the quantitative estimation of the urea the slightly modified method of S. R. Benedict and F. Gephart[1] has been employed: The urine mixed to its own volume of diluted HCl (1 to 4) has been submitted in autoclave to a pressure of 6 atmospheres (150° to 155° C.), during one and a half hours. The resulting ammonia has been determined by the Krüger-Reich-Schittenhelm[2] method, and the preformed ammonia has been substracted. The uric acid has been estimated by the E. Wörner[3] method: the precipitated urate of ammonia dissolved into a watery solution of caustic soda is placed on a water bath to drive out the ammonia. The remaining nitrogen has been finally determined by the well-known Kjeldahl method. The acetone by the Huppert-Messinger[4] method, and on account of necessary comparative estimations for other purposes the volatile fatty acid has been evaluated by the Strauss-Philippsohn method. The obtained analytical results are condensed in the following table:[5]

FIRST SERIES. NORMAL CONDITION.

Days.	Volume. c.c.	NH_3 gm.	Total N. gm.	Urea. gm.	Uric acid. gm.	Acetone. mg.	Hepatic coefficient. per 100.
1st . . .	1235	0.610	6.003	9.687	0.345	7.0	75.0
2d . . .	1344	0.635	6.523	11.068	0.411	5.0	79.0
3d . . .	1255	0.476	6.036	10.629	0.361	8.0	77.0
4th . . .	1251	0.540	5.827	10.511	0.385	3.0	84.0
5th . . .	1460	0.613	6.428	11.443	0.415	3.0	82.0
6th . . .	1154	0.498	5.722	9.743	0.342	9.0	79.0
7th . . .	1422	0.541	6.645	10.772	0.388	5.0	75.0
Averages	1303	0.559	6.169	10.5504	0.378	5.7	78.7

[1] Jour. of Am. Chem. Soc., XXX, 1760.

[2] Abderhalden, E., Physiologisches Praktikum, Berlin, 1912, p. 130.

[3] Hoppe-Seyler's Handbuch der physiol- und pathol- chemischen Analyse, Berlin, 1903, pp. 448–449.

[4] Strauss, H., and Philippsohn, H., Zeitschr. f. klin. Med., xi, 369.

[5] Delgado Palacios, G., Chimie pathologique tropicale de la région atlantique. Caracas. Lit. y Tip. del Comercio, pp. 219–293, 238, 103–125, 116.

SECOND SERIES. ACTION OF BUTYRATE OF AMMONIA.

Days.	Volume. c.c.	NH_3. gm.	Total N. gm.	Urea. gm.	Uric acid. gm.	Acetone. mg.	Hepatic coefficient. per 100.
1st	1816	0.581	7.753	13.442	0.365	84	80.7
2d	1858	0.411	8.122	14.989	0.410	108	85.9
3d	1928	0.404	8.501	16.701	0.328	132	91.5
4th	2304	0.405	8.533	17.344	0.321	149	94.7
5th	2905	0.362	8.956	17.545	0.344	202	91.2
6th	3044	0.392	9.008	18.042	0.309	235	93.3
7th	2525	0.663	8.898	16.938	0.486	245	88.7
Averages	2340	0.4597	8.538	16.428	0.366	165	89.4

I have already pointed out why the physiologically produced urea in this person is so small, namely, an average of 10.5 gm. with a corresponding volume of 1300 c.c. The greatest excess of urea which has been synthetized by the liver, namely, 8 gm., has developed a very powerful diuretic action. It is interesting to note that this person with a total amount 18 gm. urea has excreted 3 liters of urine, which has the physical appearance of diabetic urine, while it is of common occurrence that the majority of persons with this quantity of urea do not excrete more than half a volume. In all my experiments with a starting physiological amount of urea double this one the butyrate of ammonia has had the same diuretic effect, but not so marked as in this case.

The diuretic action of urea is a constant experimental fact, and all the authors admit it. The increase of acetone or iodoform giving compounds upon the normal deserves, in this case, a closer exaplanation. All authors agree in accepting that the volatile fatty acids, when ingested under certain conditions, are completely oxidized in the body, except in case they contain some inorganic radicle. Otto Porges'[6] memoir on the subject may be quoted as a standard monograph upon the destruction of fatty acids in the organism. When butyrate of ammonia is ingested this salt is transformed into urea and butyrate of sodium, which is totally destroyed by oxidation in the body. If the same salt is absorbed through the rectal mucous membrane it arrives immediately at the liver, where the hepatic cell changes it into urea and butyric acid, with the production of a little quantity of acetone. This last transformation has been realized by G. Embden[7] and his collaborators when they made the artificial irrigation of the liver with blood containing substances capable of giving acetone (acetogenic substances), the butyric acid being the principal between them, and certain of its derivatives. The same production of acetone has been carried out on diabetics by making them ingest acetogenic compounds.

[6] Ueber den Abbau der Fettsaüren im Organismus, Asher u. Spiro, Ergebnisse der Physiologie, 1910, p. 8.

[7] Hofmeister's Beiträge, 1904, vi, 59; Embden, G., and Karberlah, F., Hofmeister's Beiträge, 1906, xxx, 120; Embden, G., Salomon, H., and Schmidt, Fr., Hofmeister's Beiträge, viii, 129.

In this case the real interpretation of observed facts deserves a long explanation which space will not permit. Those interested in the subject may read the chapter Diabetic Pathogeny in a book I have published with the title *Tropical Pathological Chemistry* of the Atlantic region.[8]

From the experiment already referred to and others not quoted, easy to be conducted in man, we are right in concluding that the large intestine absorption of butyrate of ammonia produces the increased excretion of urea, acetone, and urinary volume. All the effects here observed, no doubt, are referable to the chemical nature of the employed salt and the way of introduction.

These premises well established, the question which now arises in the mind is whether or not in the common conditions of human life the intestinal putrefaction which constantly occurs from birth to death does or does not produce more or less abundant quantities of ammonia and volatile fatty acids, whose reabsorption would produce he formation of urea and acetone of putrefactive or extraphysiological origin. Before describing the method I have employed to verify the production and absorption of remarkable amounts of amoniacal salts of volatile fatty acids, it may be well to give a short exposition upon the nature and intensity of the chemical and bacterial phenomena which occur in the large intestine.

The intestinal flora which grows in the intestinal contents unfolds there with such a colossal development that more than 25 per cent. of the total organic matter of the feces are composed of bacterial residue. This intense bacterial life renovates incessantly. On the one hand the foodstuffs and the various excretions from the body through the gastro-intestinal tract bring the necessary aliment to its growth, and on the other the defensive forces of the intestinal mucous membrane and the noxious or antagonistic influences that certain groups of bacteria exercise upon others check this development. These conditions explain how a large proportion of dead bacterial matter may be excreted with the feces every twenty-four hours, as the fact has been evidenced by the Schmidt-Strasburger weight method: 5.3 grams of pure bacterial residue, or more than one hundred billions bacteria (calculated as Bacillus coli commune), are excreted daily.

In the small and large intestines the bacterial life exhibits great differences. While the small intestinal contents suffer the acid fermentation of the carbohydrates, it is five times more richer in water and travels with twenty-five times more rapidity than the large intestinal contents, a true normal fecal stasis taking place in the last portions of the alimentary canal. The matter becomes more and more poor in water and oxygen as a consequence of the

[8] Palacios, Loc cit.

absorption and powerful albuminous putrefaction, which commonly give it the alkaline reaction on account of the production of ammonia.

The intestinal contents have been studied chemically by various physiologists. Edwald,[9] Baumann,[10] MacFadyen, Nencki and Sieber[11] and others have made particular researches in the human intestine. The chemical composition of the small and large intestines differs in the same way as the bacteriological and physiological conditions referred to. The intestinal contents, as it has been collected through an artificial anus established at the distal end of the ileum, presents the following characteristics as they were observed by the last three authors named: the reaction was constantly acid, owing to the presence of organic acids, and notably of acetic acid. Other acids that were present were lactic, paralactic, various fatty acids, succinic, and the biliary acids. The odor but rarely suggested the existence of putrefactive changes. Indol, skatol, and phenol could not be demonstrated. Leucin and tyrosin were not found. Alcohol could always be demonstrated. Of gases, carbon dioxide was observed, and also faint traces of hydrogen sulphide, while methylmercaptan was absent. All these products of fermentation, as well as those originating from the normal action of digestive ferments, are completely oxidized and utilized for nutritive purposes.

In the large intestine, on the contrary, appear various products of the true albuminous putrefaction. The normal products of the digestive and fermentative proteolysis suffer the putrefactive degradation, and the resulting end-products, entirely abnormal in its origin and physiological character, are in greatest part eliminated with the feces or absorbed. It seems to be the biological law that all these products are not assimilated nor in any way utilized by the organisms. They are by their own nature or origin noxious or have toxic properties, and the organism, principally through the agency of its great antitoxic or defensive organ, the liver, tend to convert them into harmless substances as completely as possible. The putrefactive bacteria act on the various constructive stones of proteins, the amino-acids, following certain general chemical processes. The tryptophane or indol-amino-propionic acid, by the action of anaërobic bacteria, loses its amino (NH_2) group as NH_3. After this has been done other bacteria, endowed with some aërobic character, oxidize the remaining side chains, yielding carbonic acid and water. The residual indol or skatol is absorbed into the blood and reappears in the urine as indoxyl or skatoxyl in combina-

[9] Ueber das Verhalten des Fistelsekretes, etc. Virchow's Archiv, vol. lxxv.

[10] Die aromatischen Verbindunges im Harn und die Darmfäulniss, Zeitschr. f. physiol. Chem., vol. x.

[11] Ueber die chem. Vorgänge im menschl. Dünndarm, Arch. f. exp. Path. u. Pharm., vol. xxviii.

tion with sulphuric acid and alkalies as conjugated sulphates. The relative proportions in which these heterocyclic compounds appear in the urine depend upon the class of acting bacteria. According to Herter the Bacillus coli commune can produce indol under certain conditions and traces of skatol, while certain putrefactive bacteria produce this last substance in great abundance. According to the same author the indolacetic acid, another putrefactive or degradation product of tryptophane, is the chromogen of urorosein. Staal, Grosser, Porcher, and Hervieux believe that red skatol and urorosein are identical. Reasoning along these lines it is conceivable that, corresponding to a more remarkable change in the intestinal bacterial flora, other coloring matters may appear in the urine, as this has been observed, as a matter of fact, in the tropical and Atlantic region, where urorosein is replaced by cholerythrin.[12] Analogous transformations take place with other split products of protein. The tyrosin and phenylalanin, after having been desamided by the action of putrefactive bacteria losing ammonia, give various aromatic acids, phenol and cresol, and a small proportion of polyphenols. All these products are eliminated in the urine in the native state or in combination with sulphuric acid, glycocol or other compounds. Finally, leucin, butalanin, alanin, glycocol, asparaginic acid, glutaminic acid, and other non-aromatic amino-acids lose equally ammonia, and give rise in the intestine to various volatile fatty acids, such as capronic, valerianic, butyric, propionic, acetic, succinic, and glutaric acids. A certain part of these absorbed fatty acids may appear in the urine, increasing its amount of volatile acids only when they are absorbed in combination with the calcium, as the fact has been experimentally established.[13] Otherwise they are oxidized and destroyed. The butyric acid, which may be considered as an anaërobic and putrefactive product of the fatty amino-acids, and certain of its superior homologous derivatives yield acetone when they pass through the liver in combination with the ammonium, as the fact has been also established experimentally.

As has been summarily explained above, the production of putrefactive ammonia is a phenomenon of universal occurrence in the human large intestine. It is closely related to the formation of other putrefactive products, which are also absorbed into the blood, transformed by the liver, and excreted in the urine. As a matter of fact the presence of ammonia in the large intestinal contents has been verified by all investigators after the first Brauneck[14] researches. Therefore it is a reasonable and scientific hypothesis, in accordance with all our knowledge upon physiological

[12] Delgado Palacios, G., Why Yellow Fever is Endemic in the Tropical and Atlantic Region, Medical Record, July 25, 1914.

[13] Palacios, loc. cit.

[14] Brauneck, Mitteilungen aus der med. Klinik zu Würzburg, vol. ii.

and chemical phenomena, this reabsorption of putrefactive ammonia and its transformation into urea. If the formation of putrefactive urea really occurs in the common conditions of life, it must be accompanied by the production and excretion in the urine of a corresponding amount of acetone, the two substances originating from the same biochemical transformation, as the above experiment suggests. The two phenomena are, however, by no means indissoluble, because other ammoniacal salts of putrefactive origin may be transformed into urea without the production of acetone, such as acetate or propionate of ammonia, and others.

The quantitative estimation of ammonia in the feces has been rarely performed. Schmidt and Strasburger[15] in their fundamental work upon chemical and bacteriological composition of human feces do not mention any quantitative estimation of this substance. This may be explained by the fact that the intestinal ammonia is generally considered as an obliged phenomenon of the intestinal putrefaction without importance and intended to be eliminated in the feces. I have made quantitative estimations of fecal ammonia on many occasions. I shall only quote here those estimations which I have performed with the purpose of establishing the reabsorption of ammonia in the large intestine. The estimations have been made by two methods at the same time, the formol titration and the Krüger-Reich-Schittenhelm method. The figures obtained by the two methods are nearly equal in every case, and therefore may be accepted as reliable. The following table shows the amounts of ammonia and volatile acids obtained in those persons who were submitted to the comparative experiment:

Names.	Feces weight. gm.	Ammonia. gm.	Volatile acids n/10. c.c.
A. C.	85.5	0.0756	89.8
L. E.	144.2	0.1485	81.3
B. de T.	121.2	0.1108	139.7
P. A.	90.6	0.0539	60.8
R.	169.2	0.1900	100.3

The method I have employed to establish that ammoniacal salts of volatile fatty acids of putrefactive origin are effectively absorbed in the large intestine is founded upon the action of saline and drastic purgatives. It is well known that the first ones are absorbed in the stomach and first portion of the small intestine and afterward are excreted through the large intestinal mucous membrane. The second class of purgatives pass along the gastrointestinal canal and appear to operate more especially by a mechanical and irritative action. The special precaution has been taken to receive into ice the watery evacuations so as to prevent the

[15] Die Fäzes des Menschen, Berlin, 1910, p. 228.

ulterior putrefactive fermentation. The following table shows the results obtained in the same persons by the use of saline purgatives:

Names.	Feces weight. gm.	Ammonia. gm.	Volatile acids n/10. c.c.
A. C.	933.4	0.1433	215.5
L. E.	881.9	0.1734	
B. de T. . . .	1038.4	0.2124	252.4
P. A.	431.0	0.1223	155.6
R.	1213.5	0.2734	290.1

The drastic purgatives have produced a more pronounced action in the same individuals:

Names.	Feces weight. gm.	Ammonia. gm.	Volatile acids n/10. c.c.
B. de T. . . .	514.9	0.3167	452.0
P. A.	529.0	0.1521	184.3
R.	898.3	0.3167	552.0

These experimental researches prove evidently that there is present in the large intestine, in a given moment or during a certain time, a greater amount of ammonia and volatile fatty acids than the quantity which goes out with the feces every twenty-four hours. The differences reach easily 100 milligrams and more; and it is greater for the fatty acids.

Although these figures are quite remarkable, there are many reasons to believe that they are really greater. The production and absorption of fecal ammonia are continual and concomitant phenomena. When the intestinal contents pass the Bauhin valve and enter the large intestine the matter suffers the ammoniacal putrefaction and is five times more rich in water than when it goes out. The purgative surprises the matter as it is contained in the large intestine, in a given moment, and carries it away. Hence it is easy to infer that the drastic evacuation, although less rich in water and weight, contains a greater proportion of ammonia than the saline evacuation, as the reported figures demonstrate. The ammonia which is violently expelled through the agency of the purgatives corresponds to the ammonia produced during the time of their action, eight hours more or less, that is to say, three times smaller than the twenty-four hours' produced ammonia. And this evaluation manifestly represents a minimum, because very probably the purgative action interferes with the ammoniacal putrefaction, and the production of this substance is less pronounced than when the matter is quietly left to its anaërobic stagnation and putrefaction. The amount which is quantitative estimated in the feces represents only the residue which has not been absorbed. The difference between the two quantities corresponds to the amount which would be absorbed, in the supposition that the purgative would not have interfered with the intestinal putrefaction,

and that normal conditions of the intestinal contents would have been the same.

In the purgative evacuations from mellitus or insipidus diabetics I have determined a greater quantity of ammonia than in the normal condition. The amount of volatile fatty acids by the same method reach enormous figures in the same diseases. In these patients a greater proportion of volatile fatty acids has been also verified in the urine. I cannot explain in detail why, in these patients, the volatile fatty acids increase in so large amounts in the urine, while they do not augment above the normal when they are introduced directly into the rectum in combination with the ammonium as in the experiment refered to. I can only say that this depends upon their combination with the calcium, and that I have obtained experimentally this augmentation.[16]

The fecal reabsorption of volatile fatty acids is a known and admitted fact for a long time, and has been verified in man by the same direct method, that is, the action of drastic purgatives. Schmidt and Strasburger[17] says: "In the same person it has been possible to establish that during a three days' constipation (through voluntary checking of the urging to stool) the amounts of volatile fatty acids diminish in the feces, while the quantity of the same acids in castor-oil evacuations becomes three times larger. The observed difference proceeds evidently from quantitative changes of the fecal reabsorption." On the other hand, H. Strauss and H. Philippsohn,[18] by means of their method of estimating volatile fatty acids in the urine, have obtained the highest value in constipation comparatively with the normal condition.

The conclusion may be drawn, from the above experiments and those of other investigators, that it is scientifically correct to establish that, in the common conditions of human life and in normal subjects, a minimum of 300 mg. of ammonia is produced every twenty-four hours in the large intestine as a result of putrefactive processes; in some cases this quantity has amounted to twice as much (case B. de T.); and that this ammonia, after having been absorbed into the blood, appears in the urine as a minimum of 0.5 gram and even 1 gram of putrefactive urea. To this daily amount of putrefactive urea corresponds normally the production of several milligrams of acetone.

I cannot enter, in the present article, into all the details that this great question of putrefactive urea requires to be scientifically criticised and to be put in accord with all admitted physiological and pathological facts. I can only say that the phenomenon of putrefactive urea is not in contradiction with our knowledge on nutrition researches. The fact may have passed unnoticed even

[16] Palacios, loc. cit.
[17] Loc. cit.
[18] Neubauer-Huppert, Analyse des Harns, Wiesbaden, 1910, p. 190.

in the most strict nutritive balances. The comparison between the three values, fecal nitrogen, urinary nitrogen, and alimentary nitrogen, may have been realized without the putrefactive urea phenomenon being disclosed.

The production of acetone in the animal body is a question which actually is too far from its definitive solution. The experimental researches of Embden and his collaborators closely relates this production to butyric acid and some other simple compounds. But from what classes of substances or processes this butyric acid or compounds proceed is not known at present. Various physiologists believe that the destruction of proteins is the principal source of acetone; others attribute their origin to fat destruction. A well-observed fact is the counteraction of carbohydrares upon the production of acetone (anticetoplastic action) and also the constant increase of this substance in man during fast. The scientific criticism of all these questions would lengthen the present article beyond its proper scope; but all these facts and hypotheses may find, in the production of putrefactive acetone, a new and satisfactory explanation. The production of a small amount of acetone in the normal state, intimately related with the production of a certain amount of putrefactive urea, can receive from this conception an entirely more satisfactory explanation than its doubtful and obscure nutritive origin.

I hope the present ideas, founded on experiments carried out on man and corresponding to the common conditions of human life, will be of great importance to physiology and pathology. It would be also very satisfactory to the author to have laboratory men confirm the described experiments.

REVIEWS

A Text-book of Pathology. For Students of Medicine. By J. George Adami, M.A., M.D., F.R.S., Strathcona Professor of Pathology, McGill University, and Advisory Pathologist to the Montreal General and Royal Victoria Hospitals, and John McCrae, M.D., M.R.C.P., Lecturer in Pathology and Clinical Medicine, McGill University, Montreal, etc.; Senior Assistant Physician, Royal Victoria Hospital. Second edition, revised and enlarged; pp. 878; illustrated with 395 engravings and 13 colored plates. Philadelphia and New York: Lea & Febiger, 1914.

The new edition of this work needs no introduction to the medical profession. Adequate proof of this is to be seen in the reception that was accorded the previous edition. There are a few changes and modifications in the text, and several important additions containing the results of recent work on cellular activity and bacterial endotoxins have been added. The syllabus at the beginning of each chapter aids in reference, and many new and excellent colored plates and illustrations have been inserted.

The introductory chapter on the cell as the basis of pathology gives a very concise statement of our present knowledge of the principles underlying the structure, physiology, chemistry, and growth of the cell and its relation to the other cells composing the living organism. Considerable stress is laid upon the more recent work of Vaughan and Abderhalden on the bacterial endotoxins and the part that the specific enzymes produced by the body cells and acting upon the bacteria play in the production both of specific symptoms of a given disease and of anaphylactic shock.

It is interesting to note that the old controversy as to the pathogenic streptococci bids fair to be settled by Rosenow's recent work, in proving that a particular strain of streptococcus may be so modified by growth as to react similarly to pneumococcus, S. rheumaticus, etc.

In writing on the gastro-intestinal tract, the authors emphasize the fact that "auto-intoxication" is a "stupid misnomer" for the symptoms arising in cases of chronic constipation in which there is not the slightest evidence of indol production either by the tissue cells or digestive juices, but which usually arise from absorption of toxins produced by a low grade intestinal infection.

A new classification of neoplasm based on histogenetic principles is advocated. The more common classifications, according to histological characteristics, are held to be less scientific, because a large proportion of new growths, and clinically the most important of them, possess the character not of fully formed tissue elements but resemble one or other stages in the development of one or other tissue. Another advantage is that it tends to give the student a clearer conception of the nature of the different neoplasms, and of their derivation from the various primary germinal layers.

The authors apparently accept Mallory's views as to the morphology of the leukemias. They are classed among the atypical blastomas.

In treating nephritis, the authors use a very simple classification, because clinical observations on the basis of albumin, casts, and edema are so often at variance with pathological findings. "In the present state of our knowledge it is not often safe to predict what kind of kidney is going to be found in any given case. We have some admiration for a certain pathologist of eminence whose pathological diagnosis rests content with the simple statement that the kidneys indicate Bright's disease."

The volume is written in a style so simple and clear that, aside from its worth as a text-book, its perusal is a distinct pleasure, and it will be found of equal value to the practising physician as to the student of pathology. P. McC. K.

CASE HISTORIES IN OBSTETRICS. By ROBERT L. DENORMANDIE, A.B., M.D., Associate in Obstetrics, Harvard Medical School; Physician to Out-Patients, Boston Lying-in Hospital, Pp. 516. Boston: W. M. Leonard, 1914.

THIS work represents a recent addition to this now well-known series by a group of Boston authors. The increasing popularity of books of this nature is significant of the value of teaching medical subjects by example, as in clinical conference rather than by didactic lectures. In the volume under consideration the author has detailed the histories of seventy-three cases, each of which serves as a paradigm to illustrate some essential problem in obstetrics. When one recalls the clinical dissimilarities in a group of cases of sepsis or eclampsia, all of which must be classed under the general diagnosis of that group, it would appear that too few cases have been described. This seeming deficiency has been overcome by the addition to each section of a summary in which the principle in question is discussed at some length, the nature and presence of indications governing operative interference brought out, the prognosis and treatment reviewed, and finally the conclusions to

be drawn from the whole section stated. Collectively the summaries form a valuable compend of practical obstetrics.

By a logical arrangement of the twenty-eight sections the reader follows the child-bearing process from the diagnosis of pregnancy through normal pregnancy, labor, and the puerperium, and then takes up the abnormalities and complications of each period. There are also sections devoted to scopolamin-morphin anesthesia in labor, the use of hydrostatic dilating bags, puerperal insanity, and the care of the baby.

The book should be of value to the practitioner by stimulating him to a critical reviewing of his own cases, methods, and results; and to the student in the opportunity offered to consider the origin of indications for operations and the well-advised management of typical obstetrical cases. P. F. W.

A Clinical Study of the Serous and Purulent Diseases of the Labyrinth. By Dr. Erich Ruttin, Privatdocent in the Otological Clinic, University of Vienna. Authorized translation by Horace Newhart, A.B., M.D. Pp. 232; 25 illustrations. New York: Rebman Company, 1914.

To those who have studied under and admired the work of Dr. Ruttin in the Vienna Clinic this work will be most welcome, the more so since it is only the second complete work on the labyrinth in English. This work, as stated in the foreword by Prof. Dr. Urbantschitsh, is a presentation of the present position of that great school on the questions which are not yet thoroughly worked out or free from dispute. Unlike the other work mentioned above, Dr. Ruttin takes for granted that his readers are sufficiently advanced in the study of otology to know the normal anatomy and physiology of the labyrinth, and therefore opens his subject with the functional examination of the ear. The whole subject is treated in a very concise and brief manner; too brief and concise to be of great help to one who has not previously studied the subject, or, on the other hand, to one who has studied it deeply. For instance, but two pages are given to the examination of the cochlear function, and no definite instructions are given for making the tests or interpreting them. The work is evidently the result of the author's own experience and studies, and the only labyrinth operation mentioned is his own modification of Neumann's. Over half of the book is taken up with case histories, 108 in number, which are given in considerable detail, and which are well worth close study. The book is well illustrated, and, though written in the characteristic German style, will be of great value to otologists.

G. M. C.

THE ILEOCECAL VALVE. By A. H. RUTHERFORD, M.D. (Edin.) Pp. 62; 44 illustrations. New York: Paul B. Hoeber, 1914.

THE contents of this book constitutes a thesis for the M.D. degree submitted to the University of Edinburgh. Its chief interest and value concerns observations on a case with an artificial anus in the cecum 8 centimeters long, through which the ileocecal valve could be seen from time to time and carefully studied. The literature of the subject is reviewed, the valve studied in the dog and in thirty-two human specimens hardened in formalin. An excellent half-tone photographic illustration of each of the thirty-two human specimens is presented, the other illustrations also being good. It is interesting to learn that in addition to preventing regurgitation of feces from the large into the small bowel, the ileocecal valve has a sphincter action like that of the pylorus and internal anal sphincter to regulate the flow of semifluid feces from the small to the large bowel. Of more practical interest is the probability that enemata act not only as a foreign body, but as a stimulus to the peristalsis not only of the large intestine but also of the small intestine. The book is a valuable contribution to the literature. T. T. T.

LOCAL AND REGIONAL ANESTHESIA. By CARROLL W. ALLEN, M.D., Instructor in Clinical Surgery in Tulane University. Pp. 625; 255 illustrations. Philadelphia and London: W. B. Saunders Company, 1914.

THE ever enlarging field which is the subject of this volume is here treated in a thorough and efficient manner. Not only has the author given his readers a clear conception of the methods by which local analgesia may be obtained, but he has given them as well, in the first part of the book, an excellent summary of our knowledge of the character, uses, and relative value of the various substances which have been introduced from time to time for the purpose of producing anesthesia in limited areas of the body. Not the least valuable section of this portion of the book is that which deals with the relative toxicity of anesthetizing agents.

The greater part of the book deals with the methods of securing anesthesia in different parts of the body. The location of the nerve carrying sensory impulses is described in great detail, together with the method of reaching them with the anesthetizing needle. The descriptions are of a character which should enable the average surgeon to perform the operations in question with but little difficulty, provided he has the requisite gentleness and is willing to pay attention to detail.

Spinal analgesia and epidural injections of anesthetic agents are described, but receive less attention than does the use of peripheral injections; the comparatively recently introduced and as yet little used paravertebral anesthesia likewise receives brief consideration. For use in the spinal canal the author seems to favor the use of solutions of high specific gravity as being more easily controlled and more reliable in their movements within the canal than those of lower concentration than the cerebrospinal fluid; glucose is recommended as the means of securing this condition.

While many procedures are described which would probably not be used except by men who have had special experience in this kind of work, the general tone of the work is one of conservatism, and caution is given against attempting certain operations under the influence of a local anesthetic, as those for extensive malignant disease.

It has evidently been the author's intention to write a book which would serve as a reference volume rather than a hand-book of condensed information. In this effort he may have erred in the way of quoting too extensively from his sources of information (experimental investigations, etc.) instead of merely summarizing and giving his conclusions and individual opinions; those of his readers who are in search of ready information, and are content to trust the judgment of one with special experience rather than to make their own deductions, would have appreciated the addition of such summaries in certain instances. Yet when a sufficiently comprehensive view is taken of the work all doubt as to the author's position on the majority of these subjects disappears. S. W. M.

LOCAL ANESTHESIA. By DR. ARTHUR SCHLESINGER, Berlin. Translated by F. S. ARNOLD, B.A., M.B., B.Ch. (Oxon.) Pp. 202; 22 illustrations. New York: Rebman Company.

THE field for local anesthesia has been greatly widened in recent years and the contributions on the subject have been numerous and valuable. Only recently has it begun to appear in the clinical curriculum, so that most men in general practice are not familiar with the newer and better methods. This book will acquaint them with these methods and their technique. A chapter on the history of ths subject shows how many methods have been used and abandoned and which have prevailed. It is predicted that Bier's venous anesthesia is likely soon to displace other methods in major operations on the large joints and on the large tubular bones of the extremities. The commanding position attained by novocain among general surgeons is emphasized, and that the right of the

patient to a painless operation requires that the risks of general anesthesia should not be unduly exaggerated in favor of local. Most physicians will find it advantageous to familiarize themselves with the newer methods of inducing local anesthesia, and will find this book well adapted for the purpose. T. T. T.

CLINICAL EXAMINATION OF THE BLOOD AND ITS TECHNIQUE. By PROFESSOR A. PAPPENHEIM, Berlin. Translated and adapted from the German by R. DONALDSON, M.A., M.B., Ch.B., F.R.C.S. (Edin.), D.P.H., Pathologist to Royal Berks Hospital, Reading; late Assistant Pathologist Royal Infirmary, Bristol, and Demonstrator of Pathology, Universities of Bristol and Sheffield. Pp. 87; 5 illustrations. New York: William Wood & Company, 1914.

THIS small book, by one of the most noted hematologists, first appeared in 1911 as a chapter in Carl Neuberg's *Handbuch der Ausscheidungen und Körperflüssigkeiten*. It was later in the same year published in book form in the German, and is now presented to us in English with minor alterations to conform to the more recent publications of the author. It is essentially a manual for students and practitioners, and deals only with those things which are of primary importance in clinical methods of blood examination: staining, counting of cells, and hemoglobin estimation. The respective features of normal blood and those facts in the semiology which explain pathological blood pictures are described briefly and yet clearly. Two very helpful colored plates of normal and pathological blood cells are introduced. The index is quite exhaustive. The book is a brief summary of the important practical things known about the blood at the present time, and as such it may be highly recommended. T. G. M.

DISEASES OF INFANCY AND CHILDHOOD AND THEIR DIETETIC, HYGIENIC AND MEDICAL TREATMENT. By LOUIS FISCHER, M.D., Attending Physician to the Willard Parker and Riverside Hospitals, New York City; Attending Pediatrist to the Sydenham Hospital, etc. Fifth edition. Pp. 935; 301 illustrations and 43 plates. Philadelphia: F. A. Davis Co., 1914.

THE chief impression after reading this book is the wonder that such a mediocre production, to say the most, should have reached a fifth edition within eight years. To mention but a few of the

many defects of the book, we find that the classification, that much debated point, does not admit even the few facts which are generally recognized; that etiology, pathology, and symptomatology are illogically mixed; that the same diseases are described under different headings; that there is a widespread reversion to old fashioned subdivision and nomenclature of diseases, for example: cerebral pneumonia, diphtheroid, pseudo-appendicitis, lithemia, and so on; that most of the literature quoted likewise belongs to the distant past with a curious avoidance of many of the best authorities; and finally that the accounts of many diseases are by no means accurate or entirely trustworthy.

The articles on the acute exanthemata and diphtheria are the best in the book and give evidence of the author's wide experience with these diseases. The appendix contains much information of a practical nature, such as common laboratory technique, dietetics, local remedies, etc., which, coupled with the fact that diseases of all the special organs are considered, makes a book with a wide range and consequent strong appeal to the practitioner.

J. C. G.

THE TONSILS; FAUCIAL, LINGUAL, AND PHARYNGEAL, WITH SOME ACCOUNT OF THE POSTERIOR AND LATERAL PHARYNGEAL NODULES. By HARRY A. BARNES, M.D., Instructor in Laryngology, Harvard Medical School; Surgeon in the Department for Diseases of the Nose and Throat, Boston Dispensary; Assistant Laryngologist, Massachusetts General Hospital. Pp. 143; illustrated. St. Louis: C. V. Mosby Company, 1914.

THIS book, devoted solely to the tonsillar tissues, consists of 143 rather small pages of printed matter and numerous full-page illustrations, and covers the whole subject from embryology to the various methods of operating. It is not sufficiently detailed, however, to make it the last word on the subject of the tonsils, and the lack of systematic bibliography deprives it of some value as a book of reference. For the student and for the general practitioner it is exceedingly good, giving in a concise form the important facts concerning the tonsil. The embryology, anatomy, and the physiology are well dealt with, and show that the author's knowledge has been gained from actual experience as well as from literature. While, on the whole, the representations are trustworthy and agree with the general view of these structures, we do find a few dogmatic statements to which we must take exception; such as the author's conception that the lymph follicles of the posterior pharyngeal wall "can never be considered normal structures in the mucosa,"

and again we read "chronic abscess formation in the parenchyma of the tonsil is not uncommon."

The reproduction of the photomicrographs are good and clear, and the drawings illustrative of operative technique are even more elaborate than is absolutely necessary. G. B. W.

DIE IMMUNITÄTSWISSENSCHAFT. EINE KURZ GEFASSTE UBERSICHT ÜBER DIE BIOLOGISCHE THERAPIE UND DIAGNOSTIK FÜR AERZTE UND STUDIERENDE. Von DR. HANS MUCH. Oberarzt am Effendorfer Krankenhause. Second completely revised edition. Pp. 286; 6 plates, 7 figures and many tables in the text. Würzburg: Curt Habitzsch, 1914.

THIS work presents in brief form our present knowledge of the principles of immunity and their practical applications to diagnosis and treatment. Theoretical discussion is in the main avoided and bibliographical references are not given.

To the general principles of immunity and virulence, including anaphylaxis, 128 pages are devoted, and to immunological diagnostic reactions 85 pages. A few pages are devoted to chemotherapy, and the work closes with a chapter of 67 pages devoted to the application of the principles of immunity to specific diseases. In this last chapter a wide range of diseases of both man and animals, of bacterial and protozoan origin, are discussed as well as the application of immunity to the study of tumors. The up-to-date character of the revision is shown by the inclusion of an account of Abderhalden's protective enzyme methods and a reference to Friedmann's turtle bacillus treatment of tuberculosis. Descriptions of technique are numerous and complete. Excellent colored plates illustrate the opsonic-index method and the tuberculin and Wassermann reactions. R. M. P.

DREAMS AND MYTHS. By KARL ABRAHAMS, M.D., Berlin. Translated by William A. White, M.D., Washington. Pp. 74. New York: The Journal of Nervous and Mental Disease Publishing Co.

To those who have followed step by step the development of Freud's ideas, and those of the followers, Jung and Bleuler, this monograph on dreams and myths will appear as further evidence in corroboration of the brilliant work done by this school.

Those who have opposed these theories will find only newer absurdities, inconsistencies, and untruths.

Freud has already shown to a certain degree the psychological analogies between certain folk legends and individual phantasy. The present monograph is an attempt to compare the early myths with the phenomena of dreams. According to the author, certain phases of dream work elaborated by Freud, such as condensation, distortion, displacement, and wish fulfilment may also be noted in the myths, and the author uses the Prometheus saga in illustration.

In all times myths have been a field for speculation. Philosophers found in them a philosophic attribute, religion a moral idea, and now in turn, science seeks its interpretation and finds an answer. Abrahams has logically and clearly found a parallelism between myths and dreams. S. L.

Les Nouveaux Horizons de la Science. By H. Guilleminot, Chef des Travaux de Physique biologique à la Faculté de Médecin; Président de la Société de Radiologie médicale de Paris. Pp. 429; 55 illustrations. Paris: G. Steinheil, 1914.

The present volume, which is the third in this series of scientific publications, concerns itself with the science of living matter, especially with chemistry and morphology. In the first fifty pages the author reviews briefly the contents of the first two volumes, devoted chiefly to physics and electricity. The first half of the present volumes covers organic chemistry and the principles of metabolism, while the second half is occupied with a briefer discussion of comparative morphology. The book is distinctly not for the layman, and yet will scarcely appeal to one trained in chemistry. For it is not only not systematic but also fails of being complete. If one desires to familiarize himself with scientific French and increase his vocabulary, no book could be more satisfactory, for it is well written, clearly expressed, and typographically satisfactory. O. H. P. P.

A Doctor's Table Talk. By James Gregory Mumford, M.D., Lecturer on Surgery, Harvard University. Pp. 257. Boston and New York: Houghton Mifflin Co.

These table talks are between an elderly, wide awake country doctor, a city physician of large general and consulting practice and Scriba, the author, who is of course a surgeon. The topics under discussion are of professional and general interest, the three view points offering an abundance of material. The common sense conclusions to which these talks lead are refreshing.

Many topics of interest are threshed out by the "talkers." Among them may be found reference to the specialist, medical research, medical organization, the nurse, resident, and so on.

Lest one feel that all a doctor's interest is in things medical, political, and other questions of recent significance are rehearsed.

This book is one which may well help the physician to regain the right perspective of his life and in other hands may do much to clear up such misapprehension as exists between the medical profession and the people. A. A. H.

Étude Clinique du Sérum Antituberculeux de Vallée. Le Docteur Boureille, Ex-interne de la Maison de Nanterre, Directeur du Preventorium Antituberculeux du Boulevard Garibaldi. Pp. 50. Nemours: Bouloy.

This pamphlet contains a brief discussion of the serum treatment of pulmonary tuberculosis with special reference to Vallée's serum which it is claimed is "antimicrobic, antitoxic and antiendotoxic." The author briefly describes the results of the use of this serum in eight cases of tuberculosis of the lungs and temperature charts are given in full. It is worthy of note that alarming anaphylactic reactions occasionally followed the injections and that the author does not claim that this treatment is a cure for pulmonary tuberculosis, but only that it has a distinctly beneficial influence upon the temperature, weight and general condition in many cases.

O. H. P. P.

The Diseases of Children. By Henry Enos Tuley, M.D., Late Professor of Obstetrics University of Louisville Medical Department. Second edition; pp. 684; 109 illustrations. St. Louis: C. V. Mosby Co.

The book occupies the middle ground between the compend and the more thorough and complete work on pediatrics. In the main, it is a safe guide for the physician who desires the rudimentary knowledge requisite for practice, although the author evidently has not followed current pediatric literature very closely. He is particularly well qualified to speak upon the question of milk production, while the chapters on malaria and pellagra, and the sections on nervous and dermatological diseases possess some merit. As the second edition has been reached, this book must fulfil some useful function. J. C. G.

APPLIED PATHOLOGY IN DIAGNOSIS AND TREATMENT. By JULIUS M. BERNSTEIN, M.B., D.P.H., M.R.C.P., Assistant Physician (late Pathologist) to the West London Hospital. Pp. 395; 5 colored plates; 46 illustrations. London: University of London Press.

THIS book is designed to present to the practitioner a survey of the methods of the clinical laboratory, their general principles, their value, their interpretation, but not the details of their technique.

To the practical worker in the clinical laboratory the book is of little value; to the practitioner who desires a knowledge of merely the general nature of the various laboratory methods for the diagnosis and treatment of disease and a discussion of the conclusions that may be drawn from the laboratory reports, the book should be of much value.

The subjects considered are the blood, urine, stomach contents, feces, puncture fluids, serology, specific agglutination, complement-fixation and allergic tests, bacterin therapy, serum therapy and chemotherapy. No mention is made of methods for enumerating cells in the spinal fluid nor of the phenolsulphonephthalein test of renal function, both methods of much clinical value. Roentgen-ray studies and renal pyelography are not considered. The author's unqualified recommendation of spleen puncture for diagnostic purposes in splenomegaly will receive condemnation from many. On the whole the author presents the most important and generally accepted views in clear and readable form. J. H. A.

DISEASES OF THE RECTUM. By P. LOCKHART-MUMMERY, F.R.C.S., Senior Surgeon to St. Marks Hospital for Cancer; Surgeon to Queen's Hospital for Children, etc. Pp. 343; 102 illustrations. New York: William Wood & Co., 1914.

THERE is much in this book to commend it to the thoughtful reader. It is full and adequate without being padded, and is well illustrated by original drawings and sketches, mostly the author's own work. In the chapter on examination and diagnosis he gives a full description of the proper method of making a digital examination of the rectum, which, to one to whom it is unfamiliar, is useful knowledge, the application of which would certainly be appreciated by patients. His description of the important method of dilatation of the sphincter is also worthy of note.

On page 277 he draws attention to the fact that the failure to make an early diagnosis of malignant disease of the rectum is largely due to lack of examination on the part of the physician.

The descriptions of the operations for the various troubles are full and comprehensive. This is especially true of hemorrhoids, fistula in ano, and for malignant disease. As to etological factors in abscess about the rectum, he correctly states that only a small percentage are due to tuberculosis. He states that while fistula in ano is common in phthisical patients, it is also true that the great majority of patients with fistula in ano are not tuberculous.

He emphasizes the wisdom of cutting back the skin edges of the incision when operating for fissure and fistula in ano, so as to have no overhanging edges to interfere with drainage, and states that such wounds heal more quickly and leave less scar. Every physician should read the chapter on malignant disease, especially the part starting on page 278: "The early symptoms of cancer of the rectum."

All in all this book is a valuable addition to our shelves, and that it has the virtue of a personal narration of a man of broad experience.

G. G. R.

FOOD PRODUCTS. By HENRY C. SHERMAN, PH.D. Professor of Food Chemistry in Columbia University. Pp. 594; 36 illustrations. New York: MacMillan Co., 1914.

THIS book is devoted to a discussion of the important foods considering in connection with each: (1) its production, preparation for the market, and economical importance; (2) its proximate composition and general food value; (3) questions of sanitation, inspection, and standards of purity; (4) its digestibility and importance in nutrition. To the first of these is devoted in all about one-half the book; to the second, one-fifth; to the third, including chapters on food legislation, about one-fifth; to the fourth, about one-tenth of the book.

A full consideration of the subject of food legislation and inspection in the United States with important related court decisions is given.

The tables showing the composition of the foods include the content of water, protein, fat, carbohydrate, ash, refuse, calcium, phosphorus, iron, excess of acid or base, and caloric value. In addition the percentage of the various amino acids present in certain important proteins is given.

In discussing the nutritive value of the various foods the result of recent scientific investigations of Osborne and Mendel, Stepp, and McCullom and Davis and others are outlined, showing the peculiar value for growth and nutrition of certain fats and proteins and the importance of these in the arranging of dietaries.

The work is liberally supplied with references, and is well indexed.

All references to the chemistry of the foods are of the most elementary type and do not pre-suppose in the reader any considerable familiarity with physiological or organic chemistry. It is a book that can be heartily recommended for the medical student or practitioner as well as for those interested in food sanitation and food economics. J. H. A.

GUIDING PRINCIPLES IN SURGICAL PRACTICE. By FREDERICK EMIL NEEF, B.S., M.L., M.D. Pp. 167; 7 charts. New York: Surgery Publishing Company, 1914.

SURGICAL practice in this monograph refers to the cases operated on and, almost exclusively, to the common clean operations, one chapter being devoted to the treatment of unclean wounds. A logical working outline of the method of conducting a clean operation is given, as well as chapters on general considerations, the preparation for operation, and the post-operative care of the patient. The iodin disinfection of the field of operation is emphasized, preference being given to a combination with a second methyl salicylate solution for cleansing the field of operation, the iodin having been applied the evening before. The writer's preference for anesthol chloroform modified to increase its safety without impairing its anesthetic usefulness is not likely to meet with general approval. With few exceptions the contents of the book will appeal to most surgeons as a good working guide for the performance of most operations. T. T. T.

GOLDEN RULES OF DIAGNOSIS AND TREATMENT OF DISEASES. By HENRY A. CABLES, B.S., M.D., Professor of Medicine, College of Physicians and Surgeons. Second edition. Pp. 318. St. Louis: C. V. Mosby.

REVISED and rewritten in part with the addition of a section on infectious diseases, this second edition is presented. It is found to consist of numbers of medical facts which when grouped by the reader comprise the cardinal symptoms and physical signs of typical diseased conditions. It is offered as a means of ready reference and the goodly number of prescriptions add to its attraction in this respect.

The field of usefulness of the book must be small and if used beyond modest limits has the potentiality of more harm than good, as such conditions as gastric cancer, gastric ulcer and tuberculosis are not reducible to the statement of some dozens of facts.

The section on acute infections is well conceived and not open to like criticism. A. A. H.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Case of Diabetes Insipidus.—R. Fitz (*Arch. Int. Med.*, 1914, xv, 706), after reporting in some detail the reports of the first two cases of diabetes insipidus published, reports a case which has been under his personal observation, and particularly by reason of the fact that the application of the modern studies in renal function may throw considerable light upon the condition. The Wassermann reaction on the patient's blood serum was positive but negative in the spinal fluid. All of the modern tests for renal function were carefully carried out on the case. The author concludes that the original definition given by Frank still holds good, namely that diabetes insipidus is a long-continued, abnormally increased secretion of non-saccharine urine which is not caused by a diseased condition of the kidneys. There are three theories at present in vogue to explain the condition: (1) that it is due to faulty concentration power on the part of the kidney; (2) that it is a primary polydipsia with normal kidney function; (3) that it is a symptomatic polyuria induced by stimulation of the kidney from a variety of causes and in a certain number from hypersecretion of the hypophysis. The condition is a chronic disease not readily amenable to treatment and is apparently frequently of syphilitic origin. Each case, in the author's opinion, must be treated individually, particularly with reference to the evidence of substances which exaggerate the polyuria. Renal function tests in this case showed that the kidney was apparently normal but gave findings indicative of vascular hyposthenuria in which the bloodvessels were over-sensitive to the stimulation of sodium chloride, while other diuretic substances were inert. The case in question was not due apparently to any primary lack of ability to concentrate on the part of the kidney.

Resistance of the Erythrocytes to Saponin.—Numerous studies have shown that the varying degrees of resistance of the erythrocytes of different animals to saponin is dependent upon the cholesterin content of the cells. Investigations by MAY (*Ann. de med.*, Paris, 1914, i, 605) in various diseases have led to a similar result. Thus in pulmonary thrombosis, or typhoid fever, in which the cholesterin content is low, the resistance to saponin is diminished, as well as in ordinary jaundice cases, while in hemolytic jaundice the resistance is now increased, now lowered. It is normal in those conditions then, in which there is no abnormality in the cholesterin content of the blood. Hence by means of saponin resistance studies it may be possible to establish a group of diseases characterized by an anomaly in the lipoid content of the erythrocytes. It is probable that not colesterin alone, but the relation of cholesterin and lecithin which influences saponin resistance.

The Abderhalden Reaction in Carcinoma and Tuberculosis.—E. FRANKEL (*Deutsch. med. Wochenschr.*, 1914, xl, 589) has studied the sera of patients suffering with carcinoma and tuberculosis, using appropriate substrata. He has followed rigidly the directions given by Abderhalden in the third edition of his work in carrying out the tests. With cancer substratum from operative and autopsy material, 129 sera were examined. With a sarcoma substratum 62 sera were tested. A number of tuberculous and other sera were tested with tuberculous substrata. The results obtained were far from being specific. In fact, the reaction seemed to be unreliable for diagnostic purposes. The author is unable, as yet, to explain why his results have proved unreliable, while others have had satisfactory experience with this reaction. Possibly, he suggests, the kind of cases examined may have had something to do with the results obtained.

Spinal Fluid Cell Counts in Untreated Cases of Cerebrospinal Syphilis.—Having noted the great fluctuations in the cell counts of cases being treated by the Swift-Ellis method, MITCHELL, DARLING, and NEWCOMB (*Jour. Nerv. and Ment. Dis.*, 1914, xli, 686) made some comparative counts at regular intervals upon untreated cases, thus to ascertain the extent of fluctuation in the pleocytosis. The cases chosen were chiefly paretics in all the various stages of the disease: 34 patients in all are included in the series, upon whom 300 counts were made at intervals of two weeks. A brief history of each of the cases is given. In reviewing the results the following features become apparent. A count of three or less was found at some time in all but two of the 34 cases. These two were both far advanced paretics. Seven cases with high average counts were excitable grandiose paretics, but similar high counts were observed in those showing pronounced depression or the apparent remission of active symptoms. In several cases great variation was shown in the counts at two week intervals without there being any demonstrable change in the patient's symptoms. Low average counts may occur in all stages of the disease. The authors conclude that great variation in the cell count may be found at short intervals in any stage of paresis and that both high and low average counts may persist for months at a time in the various

stages of the malady; that the low or falling count is common but not universal before death. Since a reduction in the cell count to a normal limit frequently occurs in progressive untreated cases, a reduced cell count following treatment but accompanied by a persistent positive Wassermann reaction cannot be regarded as having valuable prognostic significance.

The Specific Cause and Cure of Pyorrhea Alveolaris.—Bass and Johns (*New Orleans Med. and Surg. Jour.*, 1914, lxvii, 456) have examined the material taken from the lesions in 87 cases of pyorrhea and have found amebæ in 85 of them. This finding was stimulated by an observation made earlier in the year at which time the same authors had observed amebæ in 7 cases of Rigg's disease. In addition to the above cases in which there could have been no mistake as to the diagnosis, the authors have examined material from the gums and teeth of 100 other normal individuals and were unable to find amebæ in a single instance. The technique for examining for amebæ is very simple and consists in the introduction of a suitable instrument such as a tooth pick or platinum loop underneath the gum, remembering that the amebæ are most numerous at the bottom of the lesion. The material removed is diluted on the slide and promptly examined with the microscope. The amebæ that have thus far been seen vary in size from about that of a leukocyte to three or four times this size. They do not possess a contractile vacuole but do contain refractile nutritive particles. There is a sharp differentiation between the endo- and ecto-sarc. Stained specimens show numerous inclusions of tissue of cellular remains, fair indications of the pathogenicity of the amebæ. Recognizing that ipecac has been employed with much success in the treatment of the amebic dysentery, the authors have experimented with the use of emetin given in doses of from ½ to 1 grain a day hypodermically. The dosage has been repeated daily for three or four days. Their results have been most gratifying. In several cases no amebæ could be found the next day after the first dose was given. The authors are unable to state yet the exact nature of the infecting organism nor how long they will be absent following emetin treatment. The length of time necessary to secure an absolute cure will doubtless depend upon many other factors and careful attention to the dental requirements of the patient.

The Early Diagnosis of Measles.—M. Grumann (*München. med. Wochenschr.*, 1914, lxi, 132) adverts to the importance of Koplik's spots in the early diagnosis of measles. The author has observed another early manifestation of the disease. On the tonsils there may be seen punctate or linear, white efflorescences approximately 3 mm. in length in the region of the lacunar depressions and also on the protuberances of the tonsils; in the latter situation linear efflorescences are more common. The author has noted that Koplik's spots and these appearances described above often appear simultaneously in the initial stages of measles. In many cases Koplik's spots alone are seen and not infrequently the tonsillar manifestations are the only early evidence of measles. The development of the rash makes the significance of the phenomena described above perfectly clear, the author says.

SURGERY

UNDER THE CHARGE OF

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Report of the Committee on the Treatment of Structural Scoliosis to the American Orthopedic Association, June, 1914.—(*Amer. Jour. of Orthop. Surg.*, 1914, xii, 5). The committee reached the following conclusions: Overcorrection of the deformity is apparently possible by means of Abbott's method in cases of severity corresponding to grade B and perhaps occasionally of grade A. If sufficient overcorrection is not secured or is not maintained long enough, partial or complete relapse usually follows, rather rapidly, the release from the corrected position. The period of retention in overcorrection, necessary for a cure is longer than formerly claimed; just how long cannot now be stated. Abbott's method has apparently given much better results in his own hands than in others although his technique appears to have been carefully followed. Forbes' method is apparently successful in overcoming rotation in some cases; the effect on the lateral bend has not yet been determined nor has it been shown that the improvement as regards rotation can be maintained. The method of Lovett and Sever shows no decided gain over older methods. A longer period of study and the inspection of a larger series of cases by the committee is desirable in order to determine accurately the value of the newer methods.

Concerning the Symptomatology and Treatment of Fracture of the Patella.—HAEBERLIN (*Zentralbl. f. Chir.*, 1914, xlii, 1585) reports a case in which he applied the observation of Dreyer (*Zentralbl. f. Chir.*, 1914, No. 22; for abstract see AMER. JOUR. MED. SCI., September, 1914, p. 448). By the application of an extension apparatus to the thigh and excluding the effect of the quadriceps femoris, Dreyer determined whether the lateral expansions of the quadriceps at the knee were completely torn or not. Haeberlin confirmed the value of Dreyer's observation. In Dreyer's case the quadriceps was not completely torn and he obtained bony union without operation. In Haeberlin's case the quadriceps was completely torn and after the application of the extension apparatus the patient could not extend the knee and raise the leg as in Dreyer's case. The separation of the fragments in Dreyer's case was 1 cm. (less than $\frac{1}{2}$ in.) and by the extension this was reduced to 2 mm. In Haeberlin's case the fragments were separated about one and a half fingers' breadth, and the fragments and torn

margins of the quadriceps were approximated by strong iodine catgut sutures. The extension apparatus was applied and 12 pounds weight employed. Primary union occurred. On the sixth day, with only 4 pounds weight extension, careful attempts at flexion of the knee were begun. Nine days after operation, 120 degrees of flexion could be obtained. Eighteen days after operation, the patient walked with a cane and at the end of twenty-eight days walked much better without a cane. Thirty-three days after operation there was still some thickening at the site of operation, the scar moved freely on the underlying tissues, the union of the fragments was apparently bony, according to the Roentgen rays, the patella was freely movable and there was no fluid in the knee-joint. The leg could be raised from the bed by the quadriceps.

Disappearance of Recurrent Mammary Sarcoma after the Removal of the Ovaries.—Toreck (*Annals of Surgery*, 1914, lx, 476) says that about ten years ago he reported a series of 7 cases in which he had done Beatson's operation, for the removal of the ovaries for mammary cancer. As a rule, the improvement, though striking, was but temporary; but in a few cases cures have been obtained. He now reports a case with cancerous nodes in the skin and subcutaneous tissue of the region of the operation for the removal of an advanced cancer of the breast which had been performed about four and a half years previously. The woman, aged fifty-seven years, returned more than five years after the operation, suffering from a fibromyoma of the uterus. A panhysterectomy was performed by Dr. Seeligman, after which the patient make an uninterrupted recovery. Toreck saw her about eight and a half months later when not a trace of the cancerous nodes could be found. At least a dozen of these had been counted before the last operation. The larger ones were slightly reddened, the smaller ones had not changed color. In his former series of cases there was improvement in every case; in one of them the tumor had disappeared almost entirely. The tumors, however, began to grow again after the lapse of six or seven months, sometimes sooner, in every case except one. In that case it had been firmly fixed to the chest wall, and became so loose after the removal of the ovaries that, about two months after this operation, he performed the radical breast operation. Fifteen months later, no signs of recurrence of the cancer could be detected. She was then suffering from severe headaches and died suddenly a few months later. It is possible that this case was cured. Toreck considers that the operation should not be entirely relegated to the heap of therapeutic rubbish, where most of us have placed it, but should be remembered in cases where we are unable to do anything better.

Linear Osteotomy.—Bradford (*Amer. Jour. Orthop. Surg.*, 1914, xii, 169) reports his results with linear osteotomy for hallux valgus, forward bending of the tibia, flexed knee, midtarsal deformity, operative dislocation of the hip-joint disease, weak ankles, multiple deformities, and round shoulders. He does not dissect down to the bone before inserting the osteotome but makes the instrument cut its way down through the soft tissues as well as the bone. He emphasizes the

advantage of a relatively small osteotome, narrower than the width of the bone to be cut. In hallux valgus linear osteotomy has the same advantage over wedge-shaped resection, as it has at the knee where the Macewen linear osteotomy is known to be preferable. The deformity of hallux valgus can easily be corrected, without mutilation of the head of the first metatarsal, in the following way: The sole of the foot is placed upon a sand bag, a small osteotome is driven from above down into the head of the first metarsal by means of a mallet and the bone divided by a linear division through its thickness and nearly through its width, the side of the concavity being the portion where the division of bone is most complete. No dissection of the skin is needed. The division of the bone should be close to the joint. The extensor tendon should be avoided as can easily be done. After this is done the toe is grasped and forced inward, securing a fracture of the remaining undivided portion of head of the metarsal. If necessary, any projecting exostoses can be removed by the osteotome on the dorsum or side of the bone and a transference of the tendon or a tenotomy of the extensor propius can be performed, if needed, though for this skin incisions are needed. Thoroughly satisfactory results both in correction and in terminal results can be expected.

Experimental Studies on Lung Extirpation.—KAWAMURA (*Deutsch. Zschr. f. Chir.*, 1914, cxxxi, 189) says that dogs continue to live in good health after the extirpation of a whole lung. If the animals are relatively young, they continue to grow, gradually, without noteworthy disturbance. Some dogs have withstood well the removal of a part of the remaining lung. The chief difficulty in lung extirpation is concerned with the care of the bronchial stump. The burial of the stump by the Willy Meyer method is a dependable procedure, but is not to be employed when the main bronchus is too short or the animal not a large one. In many dogs he amputated the lung between two large clamps, forcibly ligated the larger vessels and bronchi by perforation, and by a continuous suture made an exact closure of the wound surfaces with excellent results. The expansion of the remaining lung, which was slightly perceptible at the end of the operation, reaches its maximum at the end of thirty to sixty days. The space left by extirpation of one lung, within this time, was compensated for by displacement of the heart, enlargement of the remaining lung, elevation of the diaphragm, sinking in at the upper thoracic aperature and flattening or sinking in of the chest wall on the side operated on. The spine curved strongly to the side with its concavity on the operated side. Notwithstanding the fact that the positive pressure apparatus was employed, no fluid was observed in the thoracic cavity, as stated by Sauerbruch. Soon after the operation the remaining lung shows the picture of an acute vesicular emphysema, and after a long period a vicarious emphysema. An actual compensatory hypertrophy of the lung was always found, never a hyperplasia. The elastic fibers were much increased. The lung vessels in the beginning are distinctly dilated and later new ones are formed. The alveoli communicate with each other in a normal manner by means of pores in their walls. No enlarged or coalesced pores were found in the hypertrophied lungs. The macroscopically enlarged heart did not show demonstrable microscopical changes.

THERAPEUTICS

UNDER THE CHARGE OF

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The Use of Caramel in the Diet of Diabetics.—GRAFE (*Münch. med. Woch.*, 1914, lxi, 1433) has had excellent results with the use of grape-sugar caramelized at a temperature of 140° to 150° C. to supply carbohydrates to diabetics. The average daily amount used by him was from 150 to 200 gm., and this amount was given in brandy or coffee or in puddings. He found that grape-sugar caramel was better borne than cane-sugar caramel. The caramel is best given in fluid form and should not contain more than 3 or 5 per cent. of sugar. Grafe generally gave the caramel for periods of from two to four days, repeating it if necessary after interposed vegetable days. He reports 25 cases of diabetes treated on this plan with usually a marked beneficial action on the acidosis without appreciably increasing the glycosuria. By giving the average daily amount diabetics may obtain from 600 to 800 calories in the form of a utilizable carbohydrate. At times diarrhea was observed to follow the use of the caramel; if this occurs, it should be controlled by astringents. The author states that coma and enteritis are the only contra-indications to these large amounts of caramel.

Some Errors in the Salvarsan Treatment of Syphilis.—KROMAYER (*Deutsch. med. Woch.*, 1914, xl, 1736) says that it is admitted that mercury, in the great majority of cases of syphilis, removes the clinical symptoms of the disease with surprising promptness. In order to cure the disease it must be given intensively and for considerable periods of time and when so given mercury produces 90 per cent. of cures. With regard to salvarsan, Kromayer says that it is an undoubted fact that salvarsan removes the clinical symptoms of the disease in much the same way as mercury. After a single large dose of salvarsan or after a series of several high doses in succession, severe syphilitic relapses of a kind previously not observed may occur. He speaks especially of the so-called neuro-recidives in this connection. Death has not infrequently followed the injection of salvarsan; in some cases the injection has been immediately followed by a fatal result and in others death occurred after a considerable interval. In order to prevent untoward effects Kromayer strongly advocates that salvarsan be given in small doses over a considerable period of time. His practise is to give a total dose of two to three grams of salvarsan over a period of four to six weeks, dividing the total amount in ten or fifteen single doses. The results of such a course of treatment are fully as good as those of an intensive course of mercury of the same duration. Intensive treatment with mercury is very apt to cause loss of weight and is frequently interrupted by untoward symptoms of overdosage with the mercury, while the salvarsan treatment with these small

doses, improves the general condition and the patients gain weight. The author believes that salvarsan is contraindicated in diseases of the heart, bloodvessels, kidneys, liver, and brain, unless it be given in very minute initial dosage and increased with great caution. By giving initial doses of from 0.02 to 0.05 gm. salvarsan, he has had very encouraging results in such cases without any toxic effects. Kromayer says that his patients did not seem to do well with combined salvarsan and mercurial treatment, so now he prefers to alternate courses of each. He says there are two great drawbacks to the use of salvarsan: its high price and the inconvenience of intravenous administration. For these reasons, salvarsan ranks below mercury, in practical importance.

The Development of Artificial Pneumothorax.—BALBONI (*Boston Med. and Surg. Jour.*, 1914, clxxi, 147) points out that success in the use of this method of treatment depends on the manner in which the pneumothorax is produced and maintained. It is best to produce the pneumothorax gradually by frequent injections of nitrogen, and to bring it slowly up to the desired volume and pressure. The rapid production of a pneumothorax by large quantities of nitrogen is dangerous as it does not give the adjacent organs time to adjust themselves to the changed conditions; furthermore, the expulsion or sudden evacuation of large quantities of purulent matter may infect the sound lung. The only exception to this is in unilateral hemoptysis where it is desired to control the hemorrhage quickly. It is essential to have a free pleural cavity or one that can be made sufficiently free by subsequent injections to allow complete collapse of the lung. The other organs must be in such a condition as to be able to withstand the extra work thrown upon them. The patient ought to be in a sanatorium under the complete control of the physician. Frequent Roentgen-ray examinations are essential for the treatment. Artificial pneumothorax is not an indifferent procedure and should be undertaken only after the careful consideration of each case. The patient should be informed that the treatment is long, tedious, troublesome and expensive, and not devoid of danger.

The Treatment of Heart Involvement in Syphilis.—BROOKS and CARROLL (*Jour. Amer. Med. Assoc.*, 1914, lxiii, 1456) write concerning the treatment of syphilitic heart infections based on a study of 300 cases. They state that cases of heart involvement in early syphilis may be fully cured irrespective of the character of the lesion by vigorous specific treatment alone and independent of circulatory measures. Even well-established and late cases usually respond to treatment with care, or marked, though perhaps temporary, benefit. In most tertiary instances purely circulatory measures produce but slight benefit unless preceded by or combined with specific medication. Interrupted or inefficient treatment establishes an immunity or resistance on the part of the lesions against the specific drugs employed. Hence the importance of vigorous and carefully systematized treatment. They say that the most satisfactory treatment is one which combines the use of salvarsan with mercury and the iodids. Combined treat-

ment may be unnecessary in early cases but it is essential in late ones. Salvarsan, preferably old salvarsan, produces in most instances the quicker results. It is capable, however, of inducing serious symptoms, and in untried cases of heart involvement it should be administered in small doses until its action has been ascertained, particularly in those lesions characterized by disturbances of rhythm. The authors state that mercury alone may produce apparent cure. Best effects are secured with this drug when its form is from time to time changed. Its use appears to be indispensable in all well-established cases. The iodids are valuable adjuvants in the treatment of these cases, especially in their late stages, but they are apparently without specific action. Permanent injury to the heart must be assumed to have taken place in late cases, even though prompt response to treatment and apparent cure occurs. Successful treatment rests primarily on the recognition of the cause of the disease and on its specific treatment.

The Serum Treatment of Tetanus.—v. BEHRING (*Deutsch. med. Woch.*, 1914, xl, 1833) says that the symptoms of tetanus are due to the action of the tetanus toxin on the central nervous system. The tetanus toxin is able to reach the spinal cord by way of the nerves only by reason of its special affinity for nerve tissue. The transmission by way of the nerve is not rapid and in consequence symptoms are often delayed for considerable periods of time when the path by way of the nerve is a long one. In any case of tetanus the local focus should be excised and tetanus antitoxin should be immediately given in order to neutralize any free toxin. The passage of toxin by way of the nerves should be blocked by resection of the nerves. It is not necessary to amputate the entire limb when interruption of the nerve tract is all that is necessary. The prophylactic treatment by injections of antitoxin may simply delay the development of tetanus which may begin to actively manifest itself when the effect of the antitoxin has worn off. This fact suggests that the repeated administration of antitoxin in suspicious cases is necessary and advisable in order to control the disease.

The Roentgen Treatment of Exophthalmic Goitre.—SIELMANN (*Münch. med. Woch.*, 1914, lxi, 2132) reports 21 cases of exophthalmic goitre treated systematically with the Roentgen rays over periods of from six weeks to six months. The dosage must be very carefully controlled and must be regulated so as not to produce a dermatitis. He recommends this method of treatment when medical treatment fails to benefit before resorting to surgery. In case of no result and if surgery should become necessary the Roentgen treatment may be of great value in supplementing the operative treatment. He reports a number of cases in detail, and states that in his experience of five years with 21 cases only one patient failed to show improvement following the Roentgen treatment. He calls attention to the fact that thyroidectomy may not remove the cause of the disease, since, as yet the part played by the ovaries, the pituitary body and other glands in exophthalmic goitre may be a very important one.

PEDIATRICS

UNDER THE CHARGE OF

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Study of the Heart in Diphtheria.—W. E. HUME and S. J. CLEGG (*Quarterly Jour. of Med.*, 1914, viii, 1) investigated cardiac irregularities occurring in diphtheria by polygraphic records on 70 cases. Of these 70 cases 30 were found normal. Of the 40 cases showing irregularity, 22 showed the characteristics of a sinus arrhythmia with normal cardiac signs. The remaining 18 cases form the basis for this report and are divided into three groups, clinically, depending on the severity of the symptoms. In the first group of six cases the infection was virulent, with pallor, prostration, extensive membrane, high toxemia, etc. In this group dilatation of the heart was always obvious before the sixth day, the tension in the radials being very low. Premature contractions in auricles or ventricles usually preceded grave types of arrhythmia. The rythm of the heart frequently changed from day to day. Autopsy findings in 4 of these cases showed excess of fat in auricular muscle with increased vascularity. Ventricular muscle showed a very large quantity of fat. Group II shows clinically a marked toxemia and a copious septic membrane. Two of the cases died after six weeks and the remainder were seriously ill for long periods. The cardiac irregularities shown by these cases were auricular or ventricular extrasystoles, reversal of normal beat. In this group the heart beat remained rapid throughout the course of the disease and each case showed dilatation of the heart. The autopsy on one of the cases showed an absence of the increase of fat shown in the first group, but shows scattered patches of interstitial myocarditis in the ventricular muscle. The third group of cases showed no toxemia and the throat condition was not severe. Irregularities in the heart occurred in all of them. These included permature systoles, compensatory pause. It is impossible to correlate the pathological lesions of Group I with the individual instances of arrhythmia. Types of arrhythmia in each individual case may vary from day to day, depend on varying pathological processes in the heart. Any form of arrhythmia of the heart except sinus arrhythmia in diphtheria indicates that heart muscle or nerves are involved in a pathological process however mild the illness may be and special precautions necessary to keep patient recumbent.

Anaphylaxis and Status Lymphaticus: Their Relation to Disease in Infancy and Childhood.—C. MCNEIL (*Edinburgh Med. Jour.*, 1914, xiii, 38) discusses intensified pneumonia and tuberculosis in childhood which are described by the word "hypersensitiveness," and in which were found postmortem evidences of status lymphaticus. The propositions discussed are as follows: (1) that these fulminant types of illness are clinical illustrations of the pathological condition, anaphylaxis;

(2) that the status lymphaticus which was present is essentially connected with the distorted and intensified type of illness. McNeil describes anaphylaxis as a bodily condition in which abnormal reactions follow repeated injection of a substance which at first injection produced no apparent disturbance of health. Under clinical examples of general anaphylaxis he mentions serum disease, with its ordinary accelerated and immediate reactions, food anaphylaxis such as urticarias and edemas, pollen asthma as in hay fever and acute infectious diseases, the smptoms of onset of which Von Pirquet, Schick and others regarded as anaphylactic. McNeil emphasizes that both in the ordinary and the fulminant pneumonia the symptoms of onset are anaphylactic. Under clinical examples of local anaphylaxis the cutaneous and conjunctival tuberculin reactions are cited and the author submits that in the local reactions of scrofula we have an exaggerated form of local anaphylaxis, similar to the general anaphylactic reaction in fulminant pneumonia. These alleged instances of clinical anaphylaxis are similar pathologically accepted instances of anaphylaxis whose leading pathological features are vasomotor paresis, constriction of certain types of non-striped muscle, edema of the loose connective-tissue, destruction of the more delicate body epithelia and the production of these changes by very small doses of virus. The pathological similarity is here described separately and in detail using fulminant pneumonia and scrofula as examples. Discussing the weakness of the virus the disproportion of cause and effect is seen in human anaphylaxis, as in the sting of an insect or the local reaction by tuberculin or by the tertiary stage of syphilis, of which McIntosh says, "the extensive lesions without Spirocheta pallida in any number must be due to minute quantities of syphilitic toxin on highly sensitized tissues." The author claims that in fulminant pneumonia the virus is weak because of the great number of similar non-fatal cases also observed and that the fatal issue was due to hypersensitive condition of the body (anaphylactic) and not to a virulent poisoning. As to scrofula, the ordinary, normal reaction of tuberculin is accepted as an anaphylactic reaction; the intense reaction in scrofula is heightened anaphylaxis. In these various features, then, of fulminant pneumonia and scrofula, which show evidence, not of intensification of the virus, but of intensified reaction to the virus, the special stamp of pathological histology and physiology is identical with that of the phenomena of anaphylaxis, both experimental and clinical.

Empyema in Children.—H. G. MELVILLE-DUNLOP (*Edinburgh Med. Jour.*, 1914, xiii, 4) gives an analysis of 98 cases of empyema in children. During the period covering these cases 861 cases of pneumonia were treated, making a proportion of one case of empyema to every 8 or 9 cases of pneumonia treated on a childrens' ward. Almost all effusions in the pleura of children under three years are of a purulent character. The liability to purulent effusion lessens from three to ten years when the tendency to serous effusion is usually established. In 79 cases under ten years, 68 were purulent; in 67 cases at ten years and over, 28 were purulent. The pneumococcus was present in pure culture in 53 per cent. of all the cases, giving pus of an opaque, greenish color, of creamy consistence and with large masses of fibrin.

Streptococcal infection came next in 16 per cent., and caused a much thinner pus with a whitish-gray deposit on standing. Mixed infection with pneumococcus and streptococcus occurred in 14 per cent. of cases. The staphylococcus alone was present in 3 per cent. of cases. The tubercle bacillus occurred in 3 per cent. of cases, but being hard to find the percentage is probably slightly higher. The fluid in the latter cases was of a turbid character. Dunlop believes that primary forms of empyema are exceptional. In only 7 per cent. of this series was there no history of an antecedent cause for the empyema. The effusion generally occurred with, or followed lobar pneumonia and was invariably purulent. It was much less frequently associated with bronchopneumonia, but frequently developed subsequently to the infectious diseases as scarlet fever, etc. In most of the cases the effusion occurred within a few days of the crisis of a pneumonia. Empyema is often overlooked and the case treated as one of atrophy or miliary tuberculosis. It should be a routine practice to examine from time to time every case not making satisfactory progress. The symptoms of the advent of empyema are usually fever, cough, vomiting, quick breathing, sweating, restlessness, and delirium. Languor, a short paroxysmal cough and rapid emaciation are more especially the symptoms in older children. Especially, the child in almost every case looks seriously ill, has an anxious, pinched appearance and is profoundly anemic. Dyspnea, as found in pneumonia does not usually occur. Leukocytosis is usually from 20,000 to 30,000. Absolute, boardy dullness at the base with a boxy percussion note at the apex and harsh exaggerated breathing above the dullness is very suspicious of pleural effusion. Loud tubular breathing is common over a purulent effusion. The commonest complication was purulent pericarditis present in 40 per cent. of the fatal cases. Exploratory puncture is frequently necessary and is attended by little risk. Under two years the prognosis is grave but after two years the mortality diminished. Pneumococcal cases over two years usually recovered but in streptococcal and mixed cases the prognosis was not so good. Early evacuation and drainage is imperative if good results are to be looked for. Where the fluid is only turbid or the infant very young and unable to stand a serious operation aspiration is best used.

Pyloric Obstruction in Infants. — C. H. MILLER (*Lancet.*, 1914, clxxxvii, 987) discussed a series of 9 cases of pyloric obstruction in infants. The ages varied from sixteen days to eighteen weeks. There were three deaths, two from intercurrent conditions and of the six recoveries five have become perfectly normal children. Sudden, forceful vomiting is characteristic. In these cases it was noteworthy that if peristalsis was violent the treatment was much easier and progress steadier. Peristalsis is a variable sign. Visible peristalsis may occur without any hypertrophy of the stomach. It should be regarded as a sign of obstruction rather than of hypertrophy. Peristalsis of the stomach is seen also in infants with vomiting and colic in which the condition is satisfactorily treated by castor oil and eliminating milk curd from the diet for a few days. These are instances of "pyloric spasm." The presence of a palpable pyloric tumor Miller is rather skeptical of,

although he has felt a cylindrical tumor in some cases during gastric peristalsis. He regards this sign rather as one of wasting than of pyloric hypertrophy. The medical treatment consists of careful and skilful nursing, keeping the patient warm, washing out the stomach, and feeding with predigested milk. To keep the patient warm a fracture cradle covered with blanket and equipped inside with an electric lamp and a thermometer is a good method. Washing out the stomach should be performed twice a day, after a week once a day. Solutions used for this purpose are warm tap water or solutions of bicarbonate of soda. Liquor pancreaticus is preferred for the purpose of digesting milk. The milk is given a teaspoonful at a time every half hour, increasing the quantity and interval according to tolerance. Virol and albulactin are valuable as additional foods later on in the treatment. For colicy pain tincture opii ♏¼ or chlorodyne ♏i three times a day are used. Belladonna is useless in this disease. Phenolphthalein is the most useful drug to use regularly for constipation. In the very cases medical treatment only can be recommended. If the child is seen early and the diagnosis is definite Miller would recommend surgical treatment provided the child had sufficient strength. Some cases can only be treated by the physician, some are better treated by the surgeon but the after-treatment becomes again medical; in either event neither will be effective without the care of a specially skilled nurse.

OBSTETRICS

UNDER THE CHARGE OF

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Acute Tetany in the Newborn.—KRUGER-FRANKE (*Zentralblatt f. Gynäkologie*, 1913, No. 2), reports the case of a patient admitted to clinic forty hours in labor. She had in a previous confinement given birth to twins, of which the first was born in breech presentation, and ten years previously she had had an operation for vaginal fixation of the uterus. When admitted to hospital the os was partly dilated, the cervix obliterated, and the child was presenting by the breech, which was high above the pelvic brim. Uterine contractions were very weak and in efficient, and full dilatation was not obtained until seventeen hours after admission to hospital. When the breech could be reached delivery was attempted, and a male child, dead and macerated, was delivered The amniotic liquid was foul smelling and stained with meconium. The second twin presented by the head, which was high above the pelvic brim, the membranes were ruptured and the child delivered by version. It was asphyxiated and had inspired some of the foul amniotic liquid, which was removed by the tracheal catheter. On the following day the child was somnolent, cried only occasionally, and had tonic cramp-like contractions of the muscles. Trismus was absent,

but opisthotonus was present. The extremities were partially flexed. The child's skin was moist and resembled wet blotting paper to the touch. The child vomited foul material and could retain nothing in the stomach. In spite of gastric lavage with salt solution, the child did not improve, and died on the evening of the second day. A complete autopsy could not be obtained, but the abdomen was opened and a piece of intestine carefully removed and sent for bacteriological examination. Streptococci were found in the bowel. The mother's puerperal period was without complication. The cause of infection was evidently the foul and infected amniotic liquid swallowed by the child during the version which preceded its birth.

The Immediate Treatment of Depressed Fractures of the Skull in the Newborn.—While this treatment is sometimes carried out in hospitals, it is not employed as often as it should be, and on each report of success it calls the attention of obstetricians to the value of the method. KOSMACK (*American Journal of Obstetrics*, February, 1913), reports 3 cases in the Lying-In Hospital of the City of New York, in which depression occurred in the cranial bones of the fetus at birth. The first patient was a primipara, aged thirty-six years, beyond term, and the transverse diameter of the head was wedged into the brim. The promontory was sharp and the anterior posterior diameter could not be readily measured. It did not seem over 10 cm. The arch of the symphysis was moderately contracted, and also the distance between the tuberosities of the ischia. The pelvis was flattened with a tendency toward the funnel-shaped. The patient had been long in labor, with the escape of amniotic liquid, and the lower uterine segment was firmly contracted over the head and neck. The cervix admitted five fingers and seemed unusually firm. It was thought best to apply the forceps, practically the high application, and after several attempts the head was finally brought through the midpelvis to the outlet, after which the blades were removed and the head delivered by expression. The child was well developed and apparently normal, weighing $9\frac{1}{2}$ pounds. It made no effort to cry, but the contractions of the diaphragm were regular but slow. On examination a depressed fracture involving the left frontal bone and a furrow over the parietal region showed where the promontory of the sacrum has pressed upon the head during delivery. The face was very slightly bruised. The genital tract in the mother had been somewhat lacerated, and this was repaired. The child's breathing was slow and labored and the heart action very slow. An attempt was made to raise the depressed fracture by inserting a corkscrew, but this failed; then a single tenaculum forceps was hooked into the depressed portion through a small puncture wound. In spite of the condition present the child recovered, and some time afterward was found in good condition without cranial deformity. In the second case there was a marked depressed fracture of the left frontal bone, and the overlying area was edematous. Eight hours after birth the child's condition was good and respirations regular—about eighteen to the minnte. It did not cry, the lids remained separated, the pupils were equally contracted, with a very slight reaction to light. After sterilizing the skin over the site of the fracture, the hook of a single bladed Bullet forceps was inserted into the skin over the fracture and

carried down to the bone. The depressed fragments were readily raised, and on the following day the child seemed normal and made a complete recovery. In the third case the depressed fracture was concealed by a large caput, so that several days elapsed before a diagnosis was made. The outlet of the mother's pelvis was considerably contracted. It was suspected that the child had sustained injury after delivery. The operation was done as in the preceding case, but the operation was not performed until ten days after the birth of the child, when elevation was secured by a hook introduced through the cleft in the bone. The child did well and only a slight ridge could afterward be felt along the line of fracture.

Infection by the Bacillus Coli Communis Complicating Pregnancy and the Puerperal State.—SIMPSON and BERNSTEIN (*British Med. Jour.*, April 4, 1914) found that in this condition the diagnosis must be made between bacilluria, sapremia, septicemia, and septic phlebitis. The diagnosis is made by examining the blood and the urine taken by catheter, and the contents of the interior of the uterus and the cervix, obtained by swabs. If the serum be examined the agglutination reaction is often well developed with the Bacillus coli diluted to four-hundredfold. As regards treatment the pyelonephritis of pregnancy is recognized as a grave condition which may require local treatment. In general infection vaccines may be employed, the results may usually be divided into three groups: (1) where cure follows, the bacilli disappearing from the urine; (2) the symptoms are relieved and the bacilli disappear so long as the patient is kept under treatment, but to maintain the improvement vaccines must be given at increasing intervals of time; (3) the condition may subside and the bacteria remain in the bladder as harmless saprophytes. The usual methods of treating the urinary tract are described and the writers in using autogenous vaccines do not believe that they can be of value when stock vaccines of the Bacillus coli communis are employed. To be successful, vaccines must be prepared from the organism of the patient, because the Bacillus coli communis undergoes essential change when it leaves its usual location in the intestine. Three cases are described, treated successfully by these methods. In preparing vaccines the cultures were made immediately, and in ten hours sufficient growth was obtained to proceed with the preparation of the vaccines. The first doses were diluted with 0.5 per cent. lysol in normal salt solution and sterilized at 60° C., incubated for a few hours, and again heated to 60° C., and were thus ready for use within twenty-four hours after seeing the patient. The three cases reported were private cases and the most of the work done in the houses of the patients, thus demonstrating the advantages of modern methods in private practice.

The Management of the Third Stage of Labor with Special Reference to the Manual Removal of the Placenta.—AHLFELD (*Ztschrft. f. Geb. u. Gyn.*, Band 76, Heft 1, 1914) concludes from his study of this subject that the less the uterus is disturbed after the expulsion of the child, the more perfectly does the separation proceed, with but normal and physiological hemorrhages. The uterus does not virtually contract until from one and a half to two hours after childbirth. During this

time the expression of the placenta by external pressure can almost always be carried out with a minimum of disturbance. When there is no indication for shortening this period, one may wait until the uterus contracts and the placenta descends into the pelvis for any reasonable time. With primiparæ this method is sufficient in 89 per cent., with multiparæ in 75 per cent. In cases where there is the history of previous complications in labor, it may be best to shorten the third stage. This is especially true in multiparæ. Where active interference is not demanded the condition of the uterus should be watched by placing the hand upon the abdomen, and the normal separation of the placenta be observed. Where there is no external bleeding, and the uterus contracts at intervals efficiently, separation and descent of the placenta are usually complete in from one and a half to two hours, and the placenta can then be readily espressed. When sudden hemorrhage develops the discharge should be observed every five minutes and fresh gauze used, to watch the quantity of blood. The manual removal of the placenta is seldom necessary and is to be conducted, under strict antiseptic precautions, as a surgical procedure.

GYNECOLOGY

UNDER THE CHARGE OF
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Gummatous Ulceration of the Vagina.—An unusual case of syphilitic lesions in the vagina is reported by Bollag (*Cor.-bl. f. Schw. Aerzte*, 1914, xliv, 1068). The patient was a nullipara, aged forty-four years, who admitted having contracted a venereal disease at the age of twenty-one. She complained of pruritis and ulceration about the vulva, and on examination showed the presence of several old scars on the vulva and inner sides of the thighs, with two partly healed ulcers in the vagina. Between these was a ring of marked contraction, evidently due to scar tissue. One of the vaginal ulcers was excised, and showed merely inflammatory tissue. It was possible from the microscopic examination to exclude absolutely tumor formation; the histologic appearance showed nothing characteristic for any specific type of inflammation, however, such as tuberculosis or syphilis, but in spite of a negative Wassermann, the clinical appearance so strongly suggested the latter condition that an energetic antiluetic treatment was begun, whereupon the ulcers promptly healed, although they were of long standing, and had resisted local treatment. The author therefore considers their syphylitic etiology as fairly certain, and believes them to be manifestations of the tertiary stage, in other words, gummatous in nature, the vaginal stricture being also undoubtedly the result of a healed lesion of similar origin.

Urinary Disturbances in Women of Nervous Origin.—Schwartz (*Zeitschr. f. Urol.*, 1914, iii, Beiheft, 346) says that while we must be very careful not to attribute disturbances of micturition to nervous conditions until we have exhausted all the modern methods of diagnoses to exclude the possibility of some local lesion, there are certain cases in which no such disturbance can be demonstrated. These women often complain of great urgency and frequency of urination except during the menstrual periods, at which times they are free of the trouble. Schwartz thinks that in many cases of this type the disturbance lies in the sympathetic innervation of the bladder, and is the result of an insufficient internal secretory activity on the part of the ovary. He believes that the internal secretion of the ovary exerts a marked influence on the pelvic nerves of the sympathetic system, and that when this secretion is present in insufficient amounts, disturbances ensue. The explanation of the relief of symptoms during menstruation is explained by the fact that at this time the ovary is at the height of its functional activity. In proof of the justice of this assumption, he says that a number of cases of this type have been completely cured by the administration of ovarian preparations.

Radium Cure of Urethral Carcinoma.—Quite a remarkable case, both because of the result produced and of the thoroughness with which it could be studied, is reported by Legueu and Chéron (*Rev. prat. d. maladies d. org. genito-urinaires*, 1914, xi, 86). The patient was a girl, aged twenty-six years, with a hopeless and extensive squamous-cell carcinoma (proved by examination of excised piece of tissue), completely surrounding the urethra, and involving all the anterior portion of the vulva and vagina. Operation was out of the question, but following a series of vaginal and intra-urethral applications of radium the tumor completely disappeared, and was replaced by a slight amount of soft, non-painful scar tissue. Unfortunately, however, as a result of the urethral applications, the entire urethra was destroyed, including the internal sphincter, leaving the girl with a permanent incontinence. She gained weight, and in spite of the incontinence remained in perfect health for two and a half years, when she absolutely insisted on operation for relief. Legueu therefore implanted both ureters into the rectum, considering any attempt at plastic work futile. The operation was followed by peritonitis, to which the patient succumed at the end of a week. A most careful autopsy was performed, numerous microscopic sections being made of the pelvic tissues and associated lymph nodes, without the slightest trace of anything suggestive of malignancy being discoverable.

Vaginal Carcinoma Following the Use of a Pessary.—In view of the large numbers of pessaries which are worn by women, who often neglect to present themselves at proper intervals for examination, it is rather surprising that we do not oftener hear of the development of malignant tumors as a consequence. The vagina seems to be an organ which is but very slightly inclined to the primary production of new growths; that such can occur, however, as the direct result of a neglected pessary, is shown by a case reported by Edelberg (*Zentlbl. f. Gyn.*, 1914, xxxviii, 265). The patient was a woman in the late sixties, who had worn

a pessary uninterruptedly for twelve years, having become tired of returning to a physician for periodic examination. At the end of that time a bloody discharge developed, as a result of which she sought medical attention, and on examination was found to have an inoperable squamous-cell carcinoma of the vagina, the growth having evidently originated on the basis of a deep ulcer at the point of impaction of the posterior limb of the pessary. As the uterus was entirely free, the growth was certainly not an extension from that organ.

Cervical Cancer in Young Girl.—A most unusual case of a well-developed cancer of the cervix in a young girl, who had never borne children, is reported by AYRES (*Amer. Jour. Obst.*, 1914, lxix, 698). The patient was seventeen years of age; she had menstruated regularly from her thirteenth year up to a few months before coming under observation, when her periods became increased in amount. Not suspecting the true condition, a physician treated her with ergot, following which she improved somewhat. The bleeding soon became uncontrollable, however, and a gynecologic examination revealed a large cauliflower mass occupying the cervical region, microscopic examination showing it to be a typical carcinoma. A radical Wertheim operation was performed, and several months later the girl was known to be in apparent health.

DISEASES OF THE LARYNX AND CONTIGUOUS STRUCTURES

UNDER THE CHARGE OF

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OF PHILADELPHIA.

Case of Spontaneous Retrogression of Cancer of the Larynx.—PUGNAT (*Arch. internat. de lar., d'otol. et de rhinol.*, Mai-Juin, 1914) reports a case of spontaneous retrogression in cancer of the larynx. Such cases are rare but are occasionally encountered. The disease occurred in a man, aged sixty years, who had been hoarse for several months. An oval, red tumor the size of a bean occupied the entire left arytenoid region and extended upon the left vocal cord which it masked entirely. A submaxillary ganglion on the left side was found enlarged to the size of a small nut and was of hard consistence. Clinical diagnosis of malignant growth was confirmed by microscopic examination of a fragment removed with cutting forceps. Surgical interference was declined by the family. Warm sprays of an aqueous solution of adrenalin 1 to 10,000 were prescribed to be used five or six times a day; and every two days instillations were made into the larynx of an oily adrenalin solution. After some weeks it was noted that the tumor had diminished notably in volume and appeared to be

atrophied; the voice had become nearly normal; the anterior two-thirds of the left vocal cord had become visible, and finally at the end of three months there was no more hoarseness. At the close of the following month the larynx had become absolutely normal and there was no trace of the tumor evident. The patient's color had become natural, the mucous membranes were no longer anemic, while the patient had regained his strength and recovered his proper weight. The submaxillary gland, however, had not diminished in volume and had even become more indurated. For several months everything continued well, but the submaxillary ganglion was still in evidence. Eleven months after the entire disappearance of the laryngeal growth, the patient returned with a submaxillary growth the size of a mandarin orange at the same place where the enlarged gland had been noted in the first instance. The larynx had remained perfectly normal. The ganglionary tumor soon acquired enormous dimensions and provoked circulatory troubles by compression of the large vessels of the neck, and at the same time the patient became feebler and cachectic. Sudden death occurred from hemorrhage of the carotid artery. Autopsy was refused. It is to be regretted the gland had not been removed before it began to enlarge.

Teratoma of the Pharynx.—Eves (*The Laryngoscope*, September, 1914) reports and depicts a teratoma removed from the pharynx of a male infant, aged fourteen months. It had been first noticed protruding from the mouth after an attack of vomiting when the child was three weeks old. Its attachment to the pharynx was by a pedicle to the right side of the posterior wall just behind the upper end of the post tonsillar pillar. It was readily seized with a hemostat on making the child gag, and was cut loose at its base with curved scissors without an anesthetic, with very little hemorrhage. Inspection forty-eight hours later revealed only a small white area about the size of a pinhead.

Tuberculosis of the Parotid Gland.—Carmody (*The Laryngoscope*, October, 1914) describes and depicts the facial appearance of a case recently under his care in a Russian-Jewish males ubject, aged twenty-four years. He also gives a resumé of all that has been written upon the subject, including reports of 4 cases in this country and 11 cases abroad, comprising all that are known so far as his knowledge extends.

Nasal Hemorrhage.—Thomfson (*The Laryngoscope*, October, 1914) reports an uncommon case of recurring nasal hemorrhage in a man, aged sixty-three years. The right inferior turbinated body was all angiomatous tissue, and there was a suppurative caries of the right middle turbinate and anterior ethmoidal cells. A number of operative procedures were practised during a period of thirteen months, including the removal of the right middle turbinate body and eventually a submucous resection for the purpose of relieving hemorrhage from the diseased septal cartilage. Since this last operation there have been no hemorrhages. The author states that if anyone has ever done a submucous resection for the cure of hemorrhage before, he has not seen a report of the case; although one case has been reported where frequent nose-bleeds were stopped by a submucous operation, but the operation had not been done for the purpose of checking them.

Bullet Wound of the Frontal Sinus and Brain.—MACKENZIE (*Pennsylvania Med. Jour.*, April, 1914) reports a case of a male, aged forty-seven years, who was shot in the middle of the forehead at close range with a 32-caliber revolver. Skiagraphy showed the bullet located in the head about one and one-quarter inches deep, while the inner wall of the sinus was splintered and depressed. The bullet was removed by operation and the inner wall of the frontal sinus was found to be fractured with the splinters presenting inward toward the brain. Two half-inch long spicules of bone had penetrated the dura and were buried about half an inch in the brain substance. These fragments were removed and the patient made an uneventful recovery.

Intermittent Claudication of the Larynx.—GAREL (*Ann. des. mal. de l'oreille, du lar., du nez et du phar.*, No. 6, 1914) reports a case of intermittent aphonia in a clerical patient, aged forty-eight years, who was at the same time a subject of claudication of the right leg. At an earlier stage of his infirmity the intermittent aphonia ensuing upon speaking did not occur during singing, but should he sing false or below the tone necessary to retain his vocal powers, he would soon be taken with a constriction of the throat followed by an aphonia of long duration. Similarly, aphonia brusquely ensued should he address a reprimand to a scholar. Within two months a new fatigue of eyesight had supervened, making it at times difficult to read or write even large characters such as are used for illustration. The writer calls attention to the analogy with the syndromes of bulbospinal myasthenia as recognized by other observers mentioned.

Radical Treatment of Stenosis of the Larynx Due to Permanent Median Position of the Vocal Cords.—CITELLI, in an elaborate paper (*Ann. des mal. de l'oreille, du lar., du nez et du phar.*, June, 1914), defends his method of cordectomy by external access as preferable to all others suggested, and cites cases and authorities in evidence.

Excision of the Vocal Cord for Recurrent Laryngeal Paralysis.—VOISLAWSKY (*Pennsylvania Med. Jour.*, November, 1914) reports a case of bilateral paralysis following an operation for goitre. After various other unsuccessful efforts, the larynx was cocainized and a Jackson bronchoscope introduced and the left vocal cord excised with a Cordes punch. For several days subsequently the patient was intubated, and he was discharged from the hospital after the wound had healed. Breathing was made easier, there was improvement in talking and the crowing was replaced by an ordinary snore. At the time of the report a white band of scar tissue replaced the excised left vocal cord and this band approximated with the right vocal cord on phonation.

Bronchopneumonic Complications After Pharyngotomies, Thyrotomies and Laryngectomies.—CASTEX (*Ann. des mal. de l'oreille, du lar., du nez et du phar.*, June, 1914) sums up the complications of four fatal observations as due to reflex pulmonic congestion toward the second day, rapid septic pneumonia from the fourth to the eighth day, pneumonia from chill, and slow bronchopulmonic infection which drags

along for from three to five weeks. These complications are especially liable to occur in alcoholic subjects. For prevention of such sequels the following technique is advised: (1) Antiseptic sprayings during three days previous to the operation; (2) putting the teeth into good condition; (3) no general anesthesia with chloroform; (4) local anesthesia; novocaine for the exterior, and cocaine for the interior; (5) operation in two sittings for laryngectomies, with attachment of the trachea to the skin; (6) a little delay after opening the trachea, in holding it open to permit the patient to expel the blood which has entered the respiratory passages, and if this be not sufficient, insufflation of air through a soft cannula; (7) no cannula to be allowed in the trachea if possible to avoid it; (8) an esophageal tube to be allowed to remain in position for eighteen days; (9) suturing of bleeding surfaces as much as possible; (10) touching with tincture of iodine the raw surfaces not coaptible; (11) dressing and draining with aseptic gauze and frequent change of the dressing; (12) seating the patient in bed and allowing him to get up when it seems reasonable.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Experimental Arterial Lesions and Cholesterin Steatosis.—A considerable work has been done in an attempt to produce arterial lesions in animals comparable to the spontaneous diseases of man. Periodically the methods to obtain these results have changed and with each new series of experiments much hope has been expressed that the human disease could be reproduced. Pressure producing drugs (adrenalin, digitalin, barium chloride, nicotin), infectious agents (B. typhosus, Staphylococcus aureus, streptococcus), organic and inorganic intoxications and mechanical alterations of the blood stream have each had their turn in occupying the interest of those studying the diseases of the arteries. More recently MANOUELIAN (*Ann. de l'Institut Pasteur*, 1913, xxvii, 7), and others, TODD (*Lancet*. 1913, May 17) have again suggested the possible influence of the sympathetic nervous system in having much to do with the arteriosclerotic process. However, a more interesting series of experiments in which positive results were not difficult to obtain in experimental animals, have been developed by the Russian school of workers. As the method consists in feeding animals with unusual diets the resulting processes in the arterial walls are spoken of as a "dietary arteriosclerosis." The lesions thus obtained

appear quite distinct from the adrenalin type of medical necrosis. IGNATOWSKI (*Virchows Arch.*, 1909, excii) first demonstrated in rabbits the production of arterial lesions by offering the animals a foreign diet. The rabbits were fed on various animal tissues and it was the author's belief that the arterial lesions resulted from the absorption of unusual protein substances. It was, however, soon demonstrated by STUCKEY (*Centralb. f. allg. Path.*, 1912, No. 21) that the protein substances had far less effect in causing arterial lesions than fatty bodies present in the tissues. His best results were obtained by feeding egg yolk or brain substances to rabbits. This author further demonstrated that neutral fats of animal or vegetable origin produced no lesions in the vessels. Equally negative were also the experiments of WESSELKIN (*Russki Wratsch*, 1912, No. 21) with pure lecithin. Thus of the fatty substances in egg yolk there remained the important cholesterin constituent as the possible factor in bringing about the lesions in the arteries. The previous work of CHALATOW (*Virchows Arch.*, 1912, ccvii) indicating liver changes with cholesterin deposits in the liver cells following the ingestion of egg yolk or brain substance, made this seem very probable. The common observation of finding cholesterol-esters in the fatty areas of the human aorta also lent support to this view. ANITSCHKOW (*Ziegler's Beiträge*, 1913, lxv) experimented with pure cholesterin and by dissolving it in sun-flower oil was able to reproduce the lesions described by Ignatowski and Stuckey. The cholesterin oil mixture was fed to rabbits by means of a catheter for a period of one to four months. The lesions appeared as macroscopic yellow plaques upon the surface of the aorta. The media was not involved. An actual thickening of the intima with the development of new cells was seen. The reaction lay on the inner side of the internal elastic lamina and on close analysis was found to consist of an unusual collection of large endothelial cells which had loaded themselves with fat. The fatty substances were doubly refractile and simulated cholesterol-esters. It would appear that the reaction in the intima was developed mainly through the aggregation of a large foreign cell and that the individual tissue elements of the intima played little part in the lesion. Inflammatory cells are wanting and there does not appear to be any evidence of hyperplasia of the connective-tissue. In the later stages the neighboring elastic tisues show degeneration and splitting of their fibres. A comparison of these experimental arterial lesions with the human types is possible only in so far as particular scleroses are concerned. There are met with in the human arteries, lesions which have similar cell and fatty changes. It must, however, be remembered that the human scleroses are of a very diverse character and that the etiological factors vary greatly. The development of peculiar arterial lesions in rabbits by cholesterin feeding must not be too hurriedly accepted with broad significance in the human.

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CONTENTS

ORIGINAL ARTICLES

The Fundamental Principles Involved in the Use of the Bone Graft in Surgery 313
By Fred H. Albee, A.B., M.D., F.A.C.S., Professor of Orthopedic Surgery, New York Postgraduate Medical School and University of Vermont, etc.

Gastric Ulcer 325
By John B. Deaver, M.D., Philadelphia.

Pain and Other Sensory Disturbances in Diseases of the Spinal Cord and Their Surgical Treatment 337
By Charles A. Elsberg, M.D., New York.

Severe Jaundice in the Newborn Child a Cause of Spastic Cerebral Diplegia 345
By William G. Spiller, M.D., Professor of Neuropathology in the University of Pennsylvania, Philadelphia.

Prevalent Fallacies Concerning Subacromial Bursitis: Its Pathogenesis and Rational Operative Treatment 351
By Walter M. Brickner, M.D., F.A.C.S., Associate Surgeon, Mount Sinai Hospital, New York.

The Clinical Interpretation of the Wassermann Reaction, with Special Reference to Cholesterinized Antigens 365
By John A. Kolmer, M.D., Dr.Ph., Professor of Pathology in the Philadelphia Polyclinic and College for Graduates in Medicine, and Jay F. Schamberg, A.B, M.D., Professor of Diseases of the Skin in the Philadelphia Polyclinic and College for Graduates in Medicine.

Colonic and Pericolonic Abnormalities 388
By Glenn I. Jones, M.D., Medical Corps, U. S. Army.

Syphilis of the Stomach 392
By William Gerry Morgan, M.D., Professor of Gastro-enterology at the Georgetown University Hospital, Washington, D. C.

The Value of Typhoid Vaccines in the Treatment of Typhoid Fever . . 406
By E. B. Krumbhaar, M.D., Physician to the Out-patient Department, and Russell Richardson, M.D., of the Ayer Clinical Laboratory.

The Physical Basis of Chronic Infections and of Recovery without Immunity 420
By A. Parker Hitchens, M.D., Glenolden, Pennsylvania.

Keratosis Pilaris of the Scalp 424
By Richard L. Sutton, M.D., Kansas City, Missouri.

Serodiagnosis of Rabies: Preliminary Report 427
By Michael G. Wohl, M.D., Philadelphia.

REVIEWS

Blood-pressure: Its Clinical Manifestations. By George William Norris, A.B., M.D. 432
The Backward Baby. A Treatise on Idiocy and the Allied Mental Deficiencies in Infancy and Early Childhood. By Herman B. Sheffield, M.D. 433
A Manual of Normal Histology and Organography. By Charles Hill, Ph.D., M.D. 434
Cunningham's Manual of Practical Anatomy. By Arthur Robison . . 434
The Germ-cell Cycle in Animals. By Robert W. Hegner, Ph.D. . . . 435
A Treatise on Diseases of the Rectum and Anus. By A. B. Cooke . . 436
Manual of the Diseases of the Eye. By Charles H. May, M.D. . . 437
Trachoma and its Complications in Egypt. By A. F. MacCallan. . . 437
Skin Grafting. By Leonard Freeman, B.S., M.A., M.D. 438
The Care and Treatment of European Children in the Tropics. By G. Montagu Harston, M.D. 439
Ophthalmoscopic Diagnosis. By C. Adam 439
Pathological Inebriety: Its Causes and Treatment. By J. W. Astley Cooper 440
The Relations of the Lachrymal Organs to the Nose and Nasal Accessory Sinuses. By Professor Dr. A. Onodi 440
Mind and Health. By Edward E. Weaver, Ph.D. 441
A Text-book on Gonorrhea and its Complications. By Dr. Georges Luys 441
An Introduction to Experimental Psychology. By C. S. Myers, M.D., ScD. 442

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D., AND ROGER S. MORRIS, M.D.

Xanthochromia in the Cerebrospinal Fluid 443
Significance of Meningeal Permeability in General Paralysis 443
Studies Concerning the Nature of Complement 444
The Oculocardiac Reflex, Especially in Epilepsy 444
Clinical Forms of Tuberculous Meningitis in Adults 445
Zeinolytic Ferments in the Blood of Pellagrins 445
Characteristics of the Blood and of the Blood Serum Following the Action of the Roentgen Rays 446
The Changes in the Leukocytes Following Injections of Tuberculin . . 446

SURGERY

UNDER THE CHARGE OF

J. WILLIAM WHITE, M.D., AND T. TURNER THOMAS, M.D.

Operation for the Removal of Ascites 447
The Treatment of Presternal Dislocation of the Clavicle 447
Treatment of Forward Dislocations of the Clavicle 448
Clinical and Experimental Studies of Hormonal and Neohormonal . . 448
Intestinal Stasis 449
A Contribution to the Surgery of the Lesser Sac of the Peritoneum . . 449
Regeneration of Cartilage and Bone, with a Special Study of These Processes as They Occur at the Chondrocostal Junction 450
The Phenolsulphonephthalein Test from the View-point of the Abdominal Surgeon 450

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.

The Intrarectal Administration of Sodium Salicylate in Acute Rheumatic Fever 451
The Present Status of Artificial Pneumothorax Therapy 451
The Treatment of Phthisis by Pulmonary Compression 452
Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis . 453
Intramuscular Injections of Blood in the Treatment of Leukemia . . 453

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND FREDERICK O. WAAGÉ, M.D.

The Vaccine Treatment of Scarlet Fever 454
Status Lymphaticus 454
The Treatment of Infantile Paralysis 455
The Cause and Significance of Nose-bleed in Childhood 455
Nervous Disturbance in Children 456

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.

Facial Paralysis after Spontaneous Labor 457
Aortitis in a Child Having Congenital Syphilis 458
Influence of Pituitrin upon the Child 458
The Pulmotor in Infantile Paralysis 459

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.

Ovarian Transplantation 460
Spontaneous Amputation of a Myomatous Uterus 461
Treatment of Anteposed Uteri 461
Influence of Menstruation on Blood Sugar 462
Intra-uterine Sterilization with Iodine in Supravaginal Hysterectomy . 463

DISEASES OF THE LARYNX AND CONTIGUOUS STRUCTURES

UNDER THE CHARGE OF

J. SOLIS-COHEN, M.D.

A Peculiar Form of Hyperplasia of the Mucous Membrane of the Upper Respiratory Tract 463
An Anaërobic Organism Associated with Acute Rhinitis 464
Hay Fever 464
Mucous Polyp of the Nasal Fossa in an Infant Aged Three Weeks . . 464
A New Modification of an Old Adenotome 464
Endonasal Radical Treatment of Chronic Suppurative Dacryocystitis . 465

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D., AND JOHN F. ANDERSON, M.D.

Tetanus and Vaccine Virus 465
A Study of Streptococci Isolated from Certain Presumably Milk-borne Epidemics of Tonsillitis Occurring in Massachusetts in 1913 and 1914 . 466
The Plague Eradication Among Ground Squirrels 466
The Friedmann Treatment for Tuberculosis 467